

10/509341

## ANTI-INFLAMMATORY MORPHOLIN-ACETAMIDE DERIVATIVES

Novel Compounds

This invention relates to novel compounds, processes for their preparation, pharmaceutical formulations containing them and their use in  
5 therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule  
10 products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

15 The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells,  
20 followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity,  
25 in which cytokine products, such as IL-4 and IL-5 released by T-helper 2 (Th2) lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie  
30 bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in  
35 trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., 338, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- ( $\alpha$ ) and CC- ( $\beta$ ) chemokines, classified according to the  
40 spacing of two conserved cysteine residues near to the amino terminus of the

chemokine proteins. Chemokines bind to specific cell surface receptors belonging to the family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date a number of CC chemokine receptors have been identified and of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells. Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., 179, 881-887 (1994), Lloyd et al., J. Exp. Med., 191, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. et al., J. Clin. Invest. 99 (2), 178-184 (1997)), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., 188, 157-167 (1998). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 receptors (for review see Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

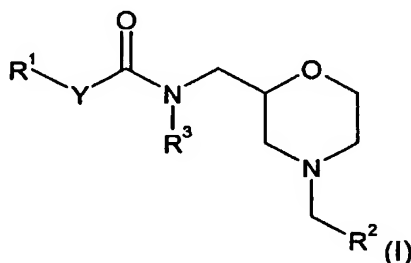
International Patent Application publication number WO 01/24786 (Shionogi & Co. Ltd.) discloses certain aryl and heteroaryl derivatives for treating diabetes. WO 00/69830 (Torrey Pines Institute for Molecular Studies) discloses

certain diazacyclic compounds, and libraries containing them, for biological screening. WO 00/18767 (Neurogen Corporation) discloses certain piperazine derivatives as dopamine D4 receptor antagonists. United States Patent 6,031,097 and WO 99/21848 (Neurogen Corporation) discloses certain  
5 aminoisoquinoline derivatives as dopamine receptor ligands. WO 99/06384 (Recordati Industria Chimica) discloses piperazine derivatives useful for the treatment of neuromuscular dysfunction of the lower urinary tract. WO 98/56771 (Schering Aktiengesellschaft) discloses certain piperazine derivatives as anti-inflammatory agents. WO 97/47601 (Yoshitomi Pharmaceutical Industries Ltd.)  
10 discloses certain fused heterocyclic compounds as dopamine D-receptor blocking agents. WO 96/39386 (Schering Corporation) discloses certain piperidine derivatives as neurokinin antagonists. WO 96/02534 (Byk Gulden Lomberg Chemische Fabrik GmbH) discloses certain piperazine thiopyridines useful for controlling helicobacter bacteria. WO 95/32196 (Merck Sharp &  
15 Dohme Limited) discloses certain piperazine, piperidine, and tetrahydropyridine derivatives as 5-HT1D-alpha antagonists. United States Patent 5,389,635 (E.I. Du Pont de Nemours and Company) discloses certain substituted imadazoles as angiotensin-II antagonists. European Patent Application publication number 0 306 440 (Schering Aktiengesellschaft) discloses certain imidazole derivatives as  
20 cardiovascular agents.

A novel group of compounds has now been found which are CCR-3 antagonists. These compounds block the migration/chemotaxis of eosinophils and thus possess anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil,  
25 basophil mast cell and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

Thus, according to one aspect of the invention, there are provided compounds of formula (I):

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wherein:

$R^1$  represents substituted or unsubstituted heteroaryl;

Y represents  $-(CR_{na}R_{nb})_n-$ ;

$R_{na}$  and  $R_{nb}$  are each independently hydrogen or  $C_{1-6}$ alkyl;

n is an integer from 1 to 5;

$R^2$  represents unsubstituted or substituted aryl or unsubstituted or

5 substituted heteroaryl;

$R^3$  represents hydrogen or  $C_{1-6}$ alkyl;

and salts and solvates thereof;

with the provisos that;

$R^1$  is not oxazolyl;

10  $R^1$  is not substituted by phenyl, and;

the following compounds are excluded;

N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(5-methoxy-2-methyl-1H-indol-3-yl)acetamide;

N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-thien-3-ylacetamide;

15 N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide;

2-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]acetamide;

N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide;

20 N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-furyl)acetamide;

2-(3-acetyl-1-benzothien-4-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]acetamide trifluoroacetate;

2-(5-bromopyridin-3-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-

25 -yl]methyl]acetamide compound with formic acid (1:1);

N-[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-furyl)acetamide;

2-(4-bromo-1H-imidazol-1-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]acetamide;

N-[[4-(3,4-difluorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-

30 -yl)acetamide;

N-[[4-(4-fluorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-

-yl)acetamide;

N-[[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-

-yl)acetamide;

35 N-[(4-{5-chlorothien-2-yl}methyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-

-thiazol-4-yl)acetamide;

N-[[4-(3-chlorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-

-yl)acetamide;

N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(5-methyl-2-pyrazin-2-yl-1,3-

40 -thiazol-4-yl)acetamide;

- methyl 2-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-2H-1,2,3-benzotriazole-5-carboxylate;  
 N-([4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl)-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)acetamide;  
 5 N-([4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl)-2-(5-pyridin-2-yl-2H-tetraazol-2-yl)acetamide;  
 N-([4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl)-2-(5-pyridin-3-yl-2H-tetraazol-2-yl)acetamide;  
 methyl 1-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-1H-1,2,3-benzotriazole-5-carboxylate compound with methyl 1-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-1H-1,2,3-benzotriazole-6-carboxylate (1:1);  
 N-(((2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl)methyl)-2-(5-methyl-2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide, and;  
 15 N-([4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl)-2-(2,3-dimethylquinoxalin-6-yl)acetamide.

Examples of the heteroaryl group, R<sup>1</sup>, include imidazolyl, triazolyl, oxadiazolyl, thiazolyl, thiophenyl, isoxadiazolyl, isoxathiazolyl, pyridinyl, furanyl, isoxazolyl, tetrazolyl and pyrazolyl.

- 20 When R<sup>1</sup> is substituted heteroaryl, suitable substituents include C<sub>1-6</sub>alkoxycarbonylamino; amino; carboxy; hydrazinocarbonyl; C<sub>1-6</sub>alkoxycarbonylhydrazinocarbonyl; C<sub>1-6</sub>alkylsulphonylamino; C<sub>1-6</sub>alkylcarbonyl; aminocarbonyl; unsubstituted heterocyclyl; heterocyclyl substituted with C<sub>1-6</sub>alkyl, halo, C<sub>1-6</sub>alkoxy, or hydroxy; unsubstituted heteroaryl; heteroaryl substituted with  
 25 C<sub>1-6</sub>alkyl, halo, C<sub>1-6</sub>alkoxy, or hydroxy; perhaloC<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkoxycarbonyl; mono- and di-(C<sub>1-6</sub>alkyl)aminocarbonyl; halo; C<sub>1-6</sub>alkoxy; nitro; C<sub>1-6</sub>alkylsulphonyl; hydroxy; C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkylthio; mono- and di-(C<sub>1-6</sub>alkyl)amino; cycloalkylaminocarbonyl; formyl; and C<sub>1-6</sub>alkylcarbonylamino.

- When R<sup>1</sup> is substituted by unsubstituted or substituted heterocyclyl,  
 30 examples of said heterocyclyl group include piperidinyl.

When R<sup>1</sup> is substituted by unsubstituted or substituted heteroaryl, examples of said heteroaryl group include pyrazinyl, oxadiazolyl, triazolyl, imidazolyl, thiadiazolyl, isoxazolyl, thiazolyl and thiophenyl.

- Suitably, R<sup>1</sup> is unsubstituted or substituted imidazolyl, unsubstituted or  
 35 substituted triazolyl, unsubstituted or substituted triazolyl, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiophenyl, unsubstituted or substituted isoxadiazolyl, unsubstituted or substituted isoxathiazolyl, unsubstituted or substituted pyridinyl, unsubstituted or substituted furanyl, unsubstituted or substituted isoxazolyl, unsubstituted or  
 40 substituted tetrazolyl and unsubstituted or substituted pyrazolyl.

When R<sup>1</sup> is substituted furanyl, suitable substituents include carboxy, C<sub>1-6</sub>alkoxycarbonylhydrazinocarbonyl, hydrazinocarbonyl, substituted heteroaryl, mono- and di-(C<sub>1-6</sub>alkyl)aminocarbonyl, C<sub>1-6</sub>alkoxycarbonyl, and C<sub>3-8</sub>cycloalkylaminocarbonyl.

- 5 When R<sup>1</sup> is substituted imidazolyl, suitable substituents include C<sub>1-6</sub>alkoxycarbonyl and halo.

When R<sup>1</sup> is substituted triazolyl, suitable substituents include C<sub>1-6</sub>alkyl and amino.

- 10 When R<sup>1</sup> is substituted oxadiazolyl, suitable substituents include C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxycarbonyl, amino, and mono- and di-(C<sub>1-6</sub>alkyl)aminocarbonyl.

When R<sup>1</sup> is substituted thiazolyl, suitable substituents include C<sub>1-6</sub>alkyl, and unsubstituted or substituted heteroaryl.

When R<sup>1</sup> is substituted isoxadiazolyl, suitable substituents include C<sub>1-6</sub>alkyl.

- 15 When R<sup>1</sup> is substituted pyrazolyl, suitable substituents include amino, C<sub>1-6</sub>alkylcarbonylamino, C<sub>1-6</sub>alkyl, perhaloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxycarbonyl, formyl, and unsubstituted heteroaryl.

When R<sup>1</sup> is substituted tetrazolyl, suitable substituents include unsubstituted heterocyclyl, for example piperidinyl, and C<sub>1-6</sub>alkyl.

- 20 When R<sup>1</sup> is substituted isoxazolyl, suitable substituents include C<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylcarbonylamino, and C<sub>1-6</sub>alkyl.

- More suitably, R<sup>1</sup> is 3-(tert-butoxycarbonylamino)pyrazol-5-yl, 3-(amino)pyrazol-5-yl, 3-(acetamido)pyrazol-5-yl, 3-(propionamido)pyrazol-5-yl, 3-(iso-propylcarbonylamino)pyrazol-5-yl, furan-2-yl, 4-(ethoxycarbonyl)-5-methylimidazol-1-yl, 5-(bromo)imidazol-1-yl, 5-methyl-1,3,4-triazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethoxycarbonyl-1,2,4-oxadiazol-5-yl, 4-(carboxy)furan-2-yl, 2,4-dimethylthiazol-5-yl, 3-(tert-butyl)isoxazol-5-yl, thiophen-2-yl, 3-methoxyisoxazol-5-yl, 4-methylthiazol-5-yl, 3,5-dimethylisoxazol-4-yl, isoxazol-3-yl, 3-methylisoxadiazol-4-yl, isoxathiazol-5-yl, 3-methylisoxazol-5-yl, 2-methylthiazol-4-yl, 5-(tert-butoxycarbonylhydrazinocarbonyl)furan-2-yl, 5-(hydrazinocarbonyl)furan-2-yl, 5-(3-methyl-1,2,4-oxadiazol-5-yl)furan-2-yl, 5-(2-methyl-1,2,4-triazol-5-yl)furan-2-yl, 3-amino-2-methyl-1,2,4-triazol-5-yl, 3-amino-1,2,4-triazol-5-yl, 3-amino-1,2,4-oxadiazol-5-yl, 4-(tert-butoxycarbonyl)pyrazol-1-yl, 2-(pyrazin-2-yl)thiazol-4-yl, 2-(methylaminocarbonyl)furan-5-yl, 2-(ethoxycarbonyl)furan-5-yl, 2-(ethylaminocarbonyl)furan-5-yl, 2-(iso-propylaminocarbonyl)furan-5-yl, 2-(cyclopropylaminocarbonyl)furan-5-yl, 2-(cyclopropylmethylaminocarbonyl)furan-5-yl, 2-(5-methyl-1,3,4-oxadiazol-2-yl)furan-2-yl, 3-(methylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(ethylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(iso-propylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 2-chlorothiophen-4-yl, 3-aminoisoxazol-5-yl, 3-acetamidoisoxazol-
- 35
- 40

5-yl, 3-propionamidoisoxazol-5-yl, 3-(*iso*-propylcarbonylamino)isoxazol-5-yl, 4-(ethoxycarbonyl)furan-2-yl, 5-(methoxycarbonyl)furan-2-yl, 4-(*iso*-propylaminocarbonyl)furan-2-yl, 4-(ethylaminocarbonyl)furan-2-yl, 4-(methylaminocarbonyl)furan-2-yl, 5-(ethylaminocarbonyl)furan-2-yl, 5-(methylaminocarbonyl)furan-2-yl, 5-(*iso*-propylaminocarbonyl)furan-2-yl, 4-(ethoxycarbonyl)furan-2-yl, pyridin-3-yl, furan-2-yl, 2-(5-methylisoxazol-3-yl)thiazol-4-yl, 2-(1-methylimidazol-5-yl)thiazol-4-yl, 2-(4-methyl-1,2,3-thiadiazol-5-yl)thiazol-4-yl, 5-methyl-2-(5-methylisoxazol-3-yl)thiazol-4-yl, 5-methyl-2-(1-methylimidazol-5-yl)thiazol-4-yl, 2-(4-methyl-1,2,3-thiadiazol-5-yl)-5-methylthiazol-4-yl, 2-(1-methylimidazol-5-yl)thiazol-4-yl, 4-methyl-2-(5-methylisoxazol-3-yl)thiazol-2-yl, 4-methyl-2-(5-methylisoxazol-5-yl)thiazol-5-yl, 3-(thiophen-2-yl)-4-(methyl)pyrazol-1-yl, 5-(*iso*-propyl)tetrazol-1-yl, 5-methyl-3-(trifluoromethyl)pyrazol-1-yl, 3-(thiazol-2-yl)pyrazol-1-yl, 5-(piperidin-1-yl)tetrazol-2-yl, 5-(piperidin-1-yl)tetrazol-1-yl, 1-(methyl)tetrazol-5-yl, tetrazol-5-yl, 5-(methyl)isoxazol-3-yl, 5-(*iso*-propyl)tetrazol-2-yl, 2-(methyl)tetrazol-5-yl, 3-(methyl)isoxazol-5-yl, 3-(formyl)pyrazol-1-yl, 3-(methyl)pyrazol-1-yl, 3,5-dimethylpyrazol-1-yl, or 4-(ethoxycarbonyl)pyrazol-1-yl.

Suitably,  $R_{na}$  and  $R_{nb}$  are both hydrogen.

Suitably,  $n$  is 1 or 2.

20 Suitably,  $R^3$  is hydrogen.

When  $R^2$  is aryl, examples include phenyl.

When  $R^2$  is substituted aryl, suitable substituents include cyano, perhalo $C_{1-6}$ alkyl, amido, halo,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxycarbonyl, mono- and di-( $C_{1-6}$ alkyl)aminocarbonyl,  $C_{1-6}$ alkoxy, nitro,  $C_{1-6}$ alkylsulphonyl, hydroxy,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylthio, mono- and di-( $C_{1-6}$ alkyl)amino, and  $C_{1-6}$ alkylcarbonylamino.

25 When  $R^2$  is heteroaryl, examples include thiophenyl.

When  $R^2$  is substituted heteroaryl, suitable substituents include cyano, perhalo $C_{1-6}$ alkyl, amido, halo,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxycarbonyl, mono- and di-( $C_{1-6}$ alkyl)aminocarbonyl,  $C_{1-6}$ alkoxy, nitro,  $C_{1-6}$ alkylsulphonyl, hydroxy,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylthio, mono- and di-( $C_{1-6}$ alkyl)amino, and  $C_{1-6}$ alkylcarbonylamino.

30 Suitably,  $R^2$  is unsubstituted or substituted phenyl or unsubstituted or substituted thiophenyl.

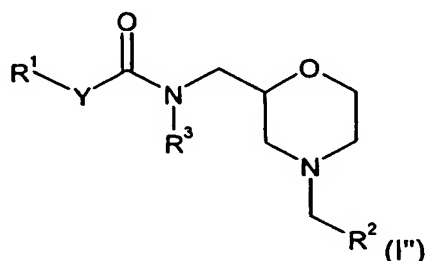
When  $R^2$  is substituted phenyl suitable substituents include halo.

When  $R^2$  is substituted thiophenyl suitable substituents include halo.

35 More suitably,  $R^2$  is phenyl substituted with chloro or fluoro, or thiophenyl substituted with chloro.

Preferably,  $R^2$  is 3-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chlorothiophen-4-yl, 3-chlorophenyl, 3,4-difluorophenyl or 3,4-dichlorophenyl.

A group of compounds of formula (I) which may be mentioned is that of  
40 formula (I''):



wherein:

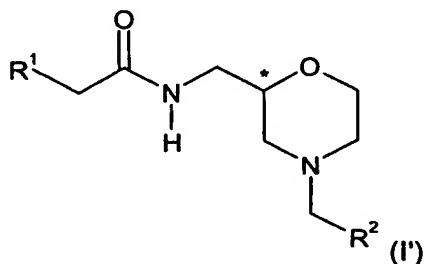
- 5         $R^1$  represents substituted or unsubstituted heteroaryl;  
        $Y$  represents  $-(CR_{na}R_{nb})_n-$ ;  
        $R_{na}$  and  $R_{nb}$  are each independently hydrogen or  $C_{1-6}$ alkyl;  
        $n$  is an integer from 1 to 5;  
        $R^2$  represents unsubstituted or substituted aryl or unsubstituted or  
 10 substituted heteroaryl;  
        $R^3$  represents hydrogen or  $C_{1-6}$ alkyl;  
       and salts and solvates thereof;  
       with the provisos that;  
        $R^1$  is not oxazolyl;  
 15         $R^1$  is not substituted by phenyl, and;  
       the following compounds are excluded;  
       N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(5-methoxy-2-methyl-1H-  
       -indol-3-yl)acetamide;  
       N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-thien-3-ylacetamide;  
 20        N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(5-methyl-1-phenyl-1H-  
       -pyrazol-4-yl)acetamide;  
       2-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-  
       -yl]methyl]acetamide;  
       N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-  
 25        -yl)acetamide;  
       N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-furyl)acetamide;  
       2-(3-acetyl-1-benzothien-4-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-  
       -yl]methyl]acetamide trifluoroacetate;  
       2-(5-bromopyridin-3-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-  
 30        -yl]methyl]acetamide compound with formic acid (1:1);  
       N-[[[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-2-(2-furyl)acetamide;  
       2-(4-bromo-1H-imidazol-1-yl)-N-[[4-(3,4-dichlorobenzyl)morpholin-2-  
       -yl]methyl]acetamide;  
       N-[[4-(3,4-difluorobenzyl)morpholin-2-yl]methyl]-2-(2-pyrazin-2-yl-1,3-thiazol-4-



- yl)acetamide;  
 N-{{4-(4-fluorobenzyl)morpholin-2-yl}methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide;  
 N-{{4-(2,3-dichlorobenzyl)morpholin-2-yl}methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide;  
 5 -yl)acetamide;  
 N-{{4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide;  
 N-{{4-(3-chlorobenzyl)morpholin-2-yl}methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide;  
 10 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl}methyl}-2-(5-methyl-2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide;  
 methyl 2-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-2H-1,2,3-benzotriazole-5-carboxylate;  
 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl}methyl}-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)acetamide;  
 15 -yl)acetamide;  
 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl}methyl}-2-(5-pyridin-2-yl-2H-tetraazol-2-yl)acetamide;  
 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl}methyl}-2-(5-pyridin-3-yl-2H-tetraazol-2-yl)acetamide;  
 20 methyl 1-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-1H-1,2,3-benzotriazole-5-carboxylate compound with methyl 1-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-1H-1,2,3-benzotriazole-6-carboxylate (1:1);  
 N-{{(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl}methyl}-2-(5-methyl-2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide, and;  
 25 N-{{4-(3,4-dichlorobenzyl)morpholin-2-yl}methyl}-2-(2,3-dimethylquinoxalin-6-yl)acetamide.

There exists a preferred subgroup of compounds of formula (I) being of formula (I')

30



wherein;

R<sup>1</sup> is unsubstituted or substituted heteroaryl, and;

R<sup>2</sup> is phenyl substituted with halo.

Suitably, R<sup>1</sup> is pyrazolyl substituted with thiophenyl, thiazolyl, formyl, C<sub>1-6</sub>alkoxycarbonyl, C<sub>1-6</sub>alkyl, or perhaloC<sub>1-6</sub>alkyl; unsubstituted tetrazolyl or tetrazolyl substituted with piperidinyl or C<sub>1-6</sub>alkyl; or isoxazolyl substituted with C<sub>1-6</sub>alkyl.

Preferably, R<sup>1</sup> is 3-(thiazol-2-yl)pyrazol-1-yl, 5-(1-piperidinyl)tetrazol-2-yl, 5-(*iso*-propyl)tetrazol-2-yl, 2-methyltetrazol-5-yl, 4-methyl-3-(thiophen-2-yl)pyrazol-1-yl, 5-(*iso*-propyl)tetrazol-1-yl, 5-methyl-3-(trifluoromethyl)pyrazol-1-yl, 5-(piperidin-1-yl)tetrazol-1-yl, 1-methyltetrazol-5-yl, tetrazol-5-yl, 3-(methyl)isoxazol-5-yl, 3-(formyl)pyrazol-1-yl, 3-(methyl)pyrazol-1-yl, 3,5-dimethylpyrazol-1-yl, 4-(ethoxycarbonyl)pyrazol-1-yl, or 5-methylisoxazol-3-yl.

Suitably, R<sup>2</sup> is phenyl substituted with chloro or fluoro.

Preferably, R<sup>2</sup> is 3,4-dichlorophenyl or 3,4-difluorophenyl.

Suitably, the stereochemistry at the position marked '\*' is (S).

Accordingly, there is provided a compound of formula (I') or a salt or solvate thereof.

Suitable compounds of the invention are Examples 1, 2, 3, 8, 12, 14, 16, 18, 19, 20, 21, 23, 25, 27, 28, 30, 31, 32, 34, 36, 40, 42, 45, 46, 48, 49, 50, 52, 53, 54, 55, 56, 58, 60, 63, 64, 65, 67, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 80, 81, 82, 83, 87, 88, 89, 90, 91, 93, 95, 97, 99, 100, 102, 104, 106, 108, 109, 110, and 111.

Preferred compounds of the invention are Examples 1, 2, 3, 19, 23, 27, 32, 34, 36, 42, 45, 48, 50, 52, 54, 58, 63, 64, 65, 67, 71, 75, 76, 78, 80, 89, 91, 93, 97, 102, 104, and 106.

More preferred compounds of the invention are Examples 1, 23, 32, 34, 36, 50, 71, 78, and 97.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates.

Examples of solvates include hydrates.

Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the stereoisomers of the compounds of formula (I), including geometric isomers and optical isomers, whether as individual stereoisomers or as mixtures thereof including racemic modifications.

Generally it is preferred that a compound of formula (I) is in the form of a single enantiomer or diastereoisomer.

Certain of the compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses  
5 all of the tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

References to 'aryl' refer to monocyclic and bicyclic carbocyclic aromatic rings, for example naphthyl and phenyl, especially phenyl.

Suitable substituents for any aryl group include 1 to 5, suitably 1 to 3,  
10 substituents selected from the list consisting of cyano, perhaloalkyl, amido, halo, alkyl, alkoxycarbonyl, mono- and di-(alkyl)aminocarbonyl, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and-di-(alkyl)amino, and alkylcarbonylamino.

References to 'heteroaryl' refer to monocyclic heterocyclic aromatic rings  
15 containing 1-4 heteroatoms selected from nitrogen, oxygen and sulphur. Examples of heterocyclic aromatic rings include imidazolyl, triazolyl, oxadiazolyl, isoxadiazolyl, isoxathiazolyl, pyridinyl, thiophenyl, furanyl, thiazolyl, pyrazinyl, tetrazolyl, triazolyl, oxadiazolyl, oxazolyl, isoxazolyl, and pyrazolyl especially imidazolyl, triazolyl, oxadiazolyl, thiophenyl, isoxadiazolyl, isoxathiazolyl, pyridinyl  
20 pyrazolyl, tetrazolyl, thiazolyl, and isoxazolyl.

Suitable substituents for any heteroaryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of alkoxycarbonylamino; amino; carboxy; hydrazinocarbonyl; alkoxycarbonylhydrazinocarbonyl; alkylsulphonylamino; alkylcarbonyl; aminocarbonyl; unsubstituted heterocyclyl;  
25 heterocyclyl substituted with alkyl, halo, alkoxy, or hydroxy; unsubstituted heteroaryl; heteroaryl substituted with alkyl, halo, alkoxy, or hydroxy; perhaloalkyl; alkyl; alkoxycarbonyl; mono- and di-(alkyl)aminocarbonyl; halo; alkoxy; nitro; alkylsulphonyl; hydroxy; alkoxyalkyl; alkylthio; mono- and-di-(alkyl)amino; cycloalkylaminocarbonyl; cyano; alkylcarbonylamino; and amido.

30 References to 'alkyl' refer to both straight chain and branched chain aliphatic isomers of the corresponding alkyl, suitably containing up to six carbon atoms.

References to 'cycloalkyl' refer to saturated alicyclic rings suitably containing 3-8 carbon atoms.

35 Suitable substituents for any cycloalkyl group include alkyl, halo, and hydroxy.

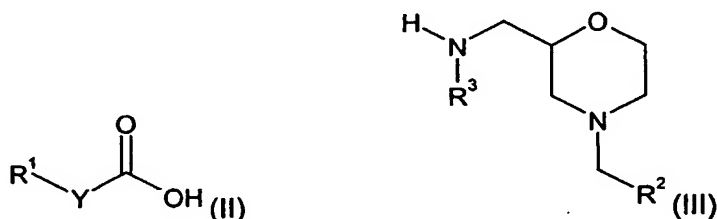
References to 'heterocyclyl' refer to monocyclic heterocyclic aliphatic rings containing 2 to 6, suitably 3 to 5, carbon atoms, and 1 to 3, heteroatoms selected from nitrogen, oxygen, and sulphur. Examples of heterocyclic rings  
40 include piperidinyl.

Suitable substituents for any heterocyclyl group include alkyl, halo, alkoxy, or hydroxy.

References to 'halogen' or 'halo' refer to iodo, bromo, chloro or fluoro, especially fluoro and chloro.

- 5 The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

Accordingly, there is provided a process for the preparation of a compound of formula (I) which process comprises the reaction of a compound of  
10 formula (II) with a compound of formula (III);



wherein;

- 15  $R^1$ , Y,  $R^3$ , and  $R^2$  are as hereinbefore defined for formula (I) in the presence of an activating agent and a peptide coupling agent, and thereafter, if required, carrying out one or more of the following optional steps:
- (i) converting a compound of formula (I) to a further compound of formula (I);
  - (ii) removing any necessary protecting group;
  - 20 (iii) preparing a salt or solvate of the compound so formed.

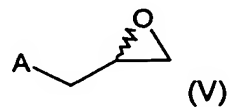
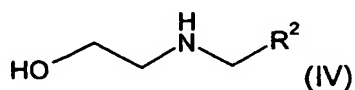
Suitably, the activating agent is 1-hydroxybenzotriazole (HOBT).

- Examples of peptide coupling agents are 1,3-dicyclohexylcarbodiimide (DCC); 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a salt thereof. Suitably, the peptide  
25 coupling agent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

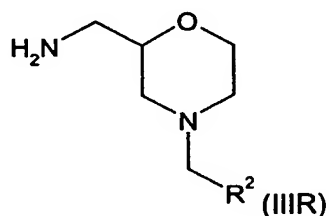
- Typically, the compound of formula (II) and the compound of formula (III) in a suitable solvent, such as a polar organic solvent, e.g. N,N-dimethylformamide are treated with a peptide coupling agent at ambient temperature, such as about 18 - 25°C. The reaction mixture is stirred at ambient  
30 temperature for an appropriate time period, such as about 12 - 20 hours.

A compound of formula (III) wherein  $R^3$  is hydrogen may be prepared either by Reaction (a) or Reaction (c). The S-enantiomer of a compound of formula (III) may be prepared by Reaction (b).

- Reaction (a). Reaction of the compound of formula (IV) with a compound of  
35 formula (V)



wherein  $R^2$  is as hereinbefore defined for formula (I) and A is a protected amino group, suitably phthalimido, followed by deprotection of the amino group to give a  
 5 compound of formula (III) wherein  $R^3$  is hydrogen i.e. a compound of formula (IIIR)



10 wherein  $R^2$  is as hereinbefore defined, and optionally resolution of the resulting enantiomers of a compound of formula (IIIR);

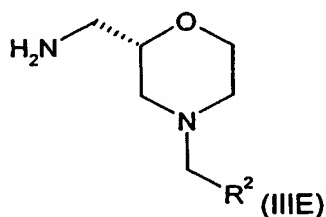
or;

Reaction (b). Reaction of a compound of formula (IV) as hereinbefore defined with a compound of formula (VA)

15

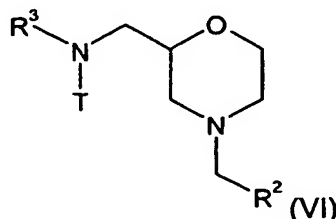


wherein A is as hereinbefore defined for formula (V), followed by deprotection of the amino group to give the corresponding enantiomer of a compound of formula  
 20 (III) wherein  $R^3$  is hydrogen i.e. a compound of formula (IIIE)



wherein  $R^2$  is as hereinbefore defined.

25 Reaction (c). Hydrolysis of a compound of formula (VI);



wherein T is trifluoroacetyl, and R<sup>3</sup> and R<sup>2</sup> are as hereinbefore defined for formula (I), and optionally resolution of the resulting enantiomers of a compound  
 5 of formula (III).

For both reactions (a) and (b), the cyclisation of the intermediate diols (IIIBR) and (IIIBE) in the reaction between the compound of formula (IV) and a compound of formula (V) or (VA) is typically carried out under the Mitsunobu conditions as follows:

10 Typically, a mixture of the compound of formula (IV) and the compound of formula (V) or formula (VA) in a suitable solvent, such as tetrahydrofuran, is stirred, suitably for 20-24 hours at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen. Further solvent is then added and the mixture cooled, suitably to 0-  
 15 5°C. A suitable phosphine, suitably triphenyl phosphine, is added and the mixture stirred until all the solid is dissolved. A suitable azo compound, suitably diisopropylazodicarboxylate, is then added over a period of time, suitably, 10-15 minutes, while maintaining the temperature at <7°C. The mixture is allowed to stand for a period of time, suitably 2-3 hours, then allowed to warm, suitably to  
 20 20-25°C. After a further period of standing, suitably 4-6 hours, further phosphine and azo compound are added. After a further period of standing, suitably 20-24 hours, the reaction mixture is concentrated to near dryness. A suitable alcohol, suitably propan-2-ol, is added and the concentration step repeated; the alcohol addition and concentration step is then repeated. Further alcohol is then added  
 25 and the mixture heated to a temperature suitably between 65-75°C. After a suitable period, suitably 20-45 minutes, the resultant slurry is cooled, suitably to 20-25°C, and then allowed to stand, suitably for 1.5 - 3 hours, after which time the product is isolated by filtration. The filter bed is washed with more alcohol and then dried *in vacuo* at 35-45°C to yield the protected form of the of formula  
 30 (IIIR) or formula (IIIE) respectively.

The removal of the protecting group from the product is typically carried out as follows. A slurry of the protected form of the of formula (IIIR) or formula (IIIE) in an appropriate polar solvent, suitably water, is heated to elevated temperature, suitably 70-75°C and then treated dropwise with a concentrated  
 35 mineral acid, suitably concentrated sulphuric acid. The mixture was then heated

at elevated temperature, suitably the reflux temperature of the solvent, for a suitable period of time, suitably 20-24 hours, after which the reaction mixture was cooled to 20-25°C and then treated with a suitable apolar solvent, suitably dichloromethane. A base, suitably 0.880 ammonia solution, is then added dropwise, maintaining the temperature between 20-25°C. Further apolar solvent is then added, the aqueous phase then being separated and extracted with further apolar solvent. The combined organic phase is washed with water and then evaporated to dryness. The residue is redissolved and the apolar solvent re-evaporated to give the compound of formula (IIIR) or formula (IIIE).

The process for the preparation of the protected form of the compound of formula (IIIR) or formula (IIIE) described above may also be undertaken in two stages, in which an intermediate compound of formula (IIIBR) or of formula (IIIBE) respectively;



wherein A is as hereinbefore defined for formulae (V) and (VA) and R<sup>2</sup> is as hereinbefore defined for formula (I);  
is isolated.

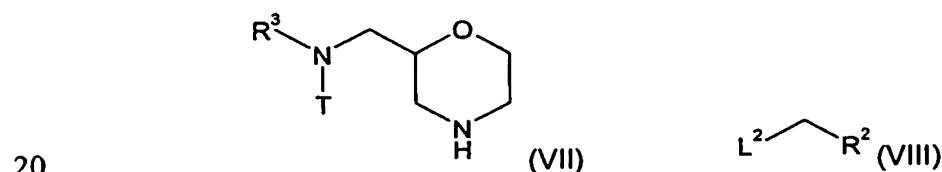
Typically, a mixture of the compound of formula (IV) and a compound of formula (V) or formula (VA) in a suitable solvent, such as tetrahydrofuran, is stirred, suitably for 20-24 hours at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen. Further compound of formula (IV) is added and the mixture heated at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen, for a suitable period of time, suitably 3-6 hours. The reaction mixture is then cooled, suitably to 20-25°C, and the compound precipitated by means of addition of a suitable co-solvent, suitably diisopropyl ether. The compound of formula (IIIBR) or formula (IIIBE) respectively is isolated by filtration, washed with further co-solvent and dried *in vacuo*.

A protected form of the compound of formula (IIIR) or formula (IIIE) may then be prepared from a compound of formula (IIIBR) or formula (IIIBE) under similar conditions to that of the reaction between a compound of formula (IV) and formulae (V) or (VA) as hereinbefore described, but omitting the reflux period prior to the addition of the phosphine and azo compounds.

Reaction (c) is typically carried out by stirring a solution of the compound of formula (VI) in a suitable solvent, for example a mixture of methanol and water, and adding a suitable base, for example potassium carbonate. The mixture is stirred at a suitable temperature, for example those in the range 20-25°C for a suitable time, for example 16-20 hours followed by removal of the organic solvent in vacuo. Water is then added and the mixture extracted with a suitable organic solvent, for example ethyl acetate. The combined organic phases are washed with water and saturated aqueous sodium chloride solution before drying over a suitable drying agent, for example sodium sulphate, filtering and evaporation of the solvent in vacuo. The crude product is then purified by flash chromatography.

The resolution of the compound of formula (IIIE) from the racemic product i.e. the compound of formula (IIIR) may be undertaken using techniques well known to those skilled in the art, for example preparative chiral high performance liquid chromatography (chiral HPLC) or by fractional crystallisation of diastereoisomeric salts.

A compound of formula (VI) may be prepared by reaction of a compound of formula (VII) with a compound of formula (VIII)



wherein;

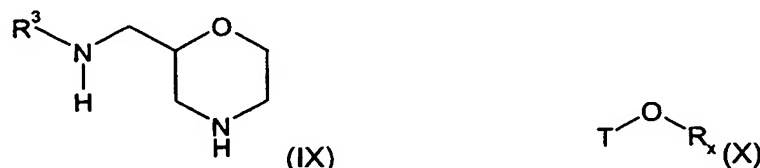
T, R<sup>3</sup> and R<sup>2</sup> are as hereinbefore defined and L<sup>2</sup> is a leaving group. A suitable leaving group, L<sup>2</sup> is a halo group such as chloro.

25 The reaction between a compound of formula (VII) and a compound of formula (VIII) is typically carried out by stirring a solution of the compound of formula (VII) in a suitable solvent, for example N,N-dimethylformamide, under an inert atmosphere, for example an atmosphere of nitrogen, with the addition of a suitable base, for example potassium carbonate, and a suitable activating agent such as sodium iodide. A solution of a compound of formula (VIII) in a suitable solvent, such as N,N-dimethylformamide, is added dropwise to the mixture. The mixture is then stirred at a suitable temperature, for example a temperature in the range of 20-25°C, for a suitable period of time, for example 16-20 hours before removing the volatile components in vacuo. The residue is partitioned between a suitable organic solvent, for example dichloromethane, and a saturated aqueous base, for example saturated aqueous sodium carbonate solution. The organic phase is then washed with additional saturated aqueous base and water before



drying over a suitable drying agent, for example magnesium sulphate, filtering and evaporation of the solvent in vacuo to yield the crude product. The crude product is purified by flash chromatography.

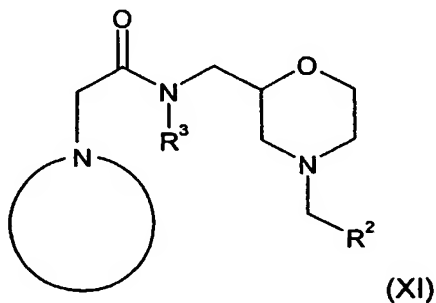
A compound of formula (VII) may be prepared by reaction of a compound  
5 of formula (IX) with a compound of formula (X);



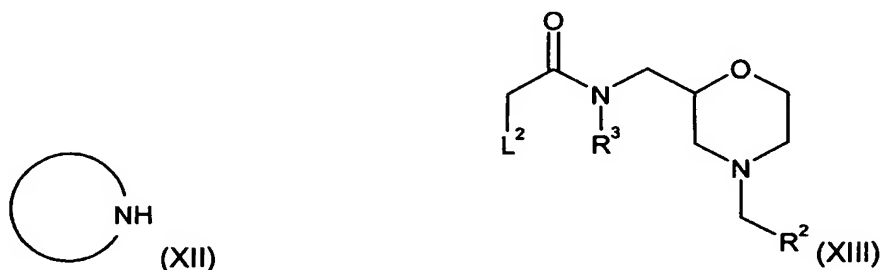
wherein  $R^3$  and T are as hereinbefore defined and  $R_x$  is an alkyl group, suitably  
10 ethyl.

The reaction between a compound of formula (IX) and a compound of  
formula (X) is typically carried out by stirring a solution of a compound of formula  
(IX) in a suitable organic solvent, for example methanol, under an inert  
atmosphere, for example an atmosphere nitrogen, and then adding a solution of  
15 a compound of formula (X) in a suitable organic solvent, for example ether. The  
mixture is then stirred for a suitable period of time, for example 20-40 minutes at  
a suitable temperature, for example a temperature in the range of 20-25°C and  
the volatile components removed in vacuo. The residue is then dissolved in a  
suitable organic solvent, for example methanol, and the volatile components  
20 removed in vacuo.

Additionally, and in a further aspect, a compound of formula (I) wherein Y  
is  $-CH_2-$  and  $R^1$  is an unsubstituted or substituted N-linked heteroaryl group i.e. a  
compound of formula (XI)



may be prepared by reaction of a compound of formula (XII) with a compound of  
formula (XIII);



wherein (XII) is an unsubstituted or substituted heteroaryl group,  $L^2$  is a leaving group, and  $R^3$  and  $R^2$  are as hereinbefore defined for formula (I), and thereafter,  
 5 if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing a salt or solvate of the compound so formed.

Suitable leaving groups are halo groups, preferably bromo.

10 Typically, the reaction between a compound of formula (XII) and a compound of formula (XIII) will be conducted in a suitable organic solvent, such as for example dichloromethane, N,N-dimethylformamide or a mixture thereof, suitably at ambient temperature, e.g. 18 - 25°C for an appropriate time period, e.g. 4 - 10h. A suitable base such as an alkali or alkaline earth metal carbonate,  
 15 e.g. potassium carbonate, is then added.

A compound of formula (XIII) may be prepared by reaction of a compound of formula (III) with a compound of formula (XIV)



20 wherein  $L^2$  is as hereinbefore defined for formula (XIII), in the presence of a peptide coupling reagent. Examples of peptide coupling agents are 1,3-dicyclohexylcarbodiimide (DCC); 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a salt thereof.  
 25 Suitably, the peptide coupling agent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Typically, the reaction between a compound of formula (III) and a compound of formula (XIV) is conducted at low temperature, e.g. 0 - 5°C, in a suitable organic solvent such as a haloalkane e.g. dichloromethane, for a suitable  
 30 time period e.g. 20 - 60 mins.

The compounds of formula (II), certain compounds of formula (III), certain compounds of formula (IV), (V), certain compounds of formula (VI), certain compounds of formula (VII), (VIII), (IX), (X), (XII), and (XIV) are known, commercially available compounds, and/or may be prepared by analogy with

known procedures, for examples those disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

The compounds of formulae (IIIBR), (IIIBE), and (XIII) are considered to  
5 be novel.

Accordingly, there is provided a compound of formula (IIIBR).

There is also provided a compound of formula (IIIBE).

There is also provided a compound of formula (XIII).

The above mentioned conversion of a compound of formula (I) into  
10 another compound of formula (I) includes any conversion which may be effected using conventional procedures, but in particular the said conversions include converting one group R<sup>1</sup> into another group R<sup>1</sup>.

The above mentioned conversion may be carried out using any appropriate method under conditions determined by the particular groups  
15 chosen. Thus, suitable conversions of one group R<sup>1</sup> into another group R<sup>1</sup> include:

(a). converting a group R<sup>1</sup> which represents unsubstituted heteroaryl group into a group R<sup>1</sup> which represents an alkylated heteroaryl group; such a conversion may be carried out using an appropriate conventional alkylating procedure, for  
20 example treating an appropriately protected compound of formula (I) with a trialkylsilyldiazomethane.

(b). converting a group R<sup>1</sup> which represents an amino substituted heteroaryl group into a group R<sup>1</sup> which represents an alkylamido substituted heteroaryl group; such a conversion may be carried out using an appropriate conventional  
25 acylation procedure, for example treating an appropriately protected compound of formula (I) with an acid chloride.

(c). converting a group R<sup>1</sup> which represents an ester substituted heteroaryl group into a group R<sup>1</sup> which represents a carboxy substituted heteroaryl group; such a conversion may be carried out using an appropriate conventional  
30 hydrolysis procedure, for example treating an appropriately protected compound of formula (I) with an aqueous base.

(d). converting a group R<sup>1</sup> which represents an ester substituted heteroaryl group into a group R<sup>1</sup> which represents an alkyloxadiazole substituted heteroaryl group; such a conversion may be carried out using an appropriate procedure, for  
35 example treating an appropriately protected compound of formula (I) with an acetamidoxime, followed by an alkoxide base.

(e). converting a group R<sup>1</sup> which represents a carboxy substituted heteroaryl group into a group R<sup>1</sup> which represents a hydrazine carboxylic acid ester substituted heteroaryl group; such a conversion may be carried out using an  
40 appropriate procedure, for example treating an appropriately protected

compound of formula (I) with an alkylcarbazide in the presence of suitable activating and coupling agents, for example 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

- (f). converting a group R<sup>1</sup> which represents a hydrazine carboxylic acid ester substituted heteroaryl group into a group R<sup>1</sup> which represents a hydrazine carboxylic acid substituted heteroaryl group; such a conversion may be carried out using an appropriate hydrolysis procedure, for example treating an appropriately protected compound of formula (I) with dilute hydrochloric acid.
- (g). converting a group R<sup>1</sup> which represents a hydrazine carboxylic acid substituted heteroaryl group into a group R<sup>1</sup> which represents an alkylloxadiazole substituted heteroaryl group; such a conversion may be carried out using an appropriate cyclisation procedure, for example treating an appropriately protected compound of formula (I) with alkylorthoacetate.
- (h). converting a group R<sup>1</sup> which represents a hydrazine carboxylic acid substituted heteroaryl group into a group R<sup>1</sup> which represents an alkyltriazole substituted heteroaryl group; such a conversion may be carried out using an appropriate cyclisation procedure, for example treating an appropriately protected compound of formula (I) with alkylacetimidate.

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected, for example those methods discussed in standard reference texts of synthetic methodology such as *P J Kocienski, Protecting Groups, (1994), Thieme*.

For any of the hereinbefore described reactions or processes, conventional methods of heating and cooling may be employed, for example electric heating mantles and ice/salt baths respectively. Conventional methods of purification, for example crystallisation and column chromatography may be used as required.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional procedures such as the fractional crystallisation of diastereoisomeric derivatives or chiral high performance liquid chromatography (chiral HPLC).

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The salts and solvates of the compounds of formula (I) may be prepared and isolated according to conventional procedures.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

5    (a) CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5µg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in  
10 binding buffer (HEPES 50 mM, CaCl<sub>2</sub> 1 mM, MgCl<sub>2</sub> 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [<sup>125</sup>I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30µM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 µl. Competition binding data were analysed by fitting the  
15 data with a four parameter logistic equation. Data are presented as the mean pIC<sub>50</sub> values (negative logarithm of the concentration of compound which inhibits [<sup>125</sup>I]eotaxin binding by 50%) from at least two experiments.

The compounds of the Examples were tested in the CCR-3 binding assay. The compounds of the Examples tested in the CCR-3 binding assay  
20 possessed pIC<sub>50</sub> values in the range 5.5 – 8.6.

(b) Eosinophil Chemotaxis Assay.

Compounds were evaluated for their inhibitory effect on eosinophil chemotaxis. Eosinophils were purified from human peripheral blood by standard CD16 cell depletion using a Miltenyi cell separation column and a magnetic  
25 Super Macs magnet as previously described (Motegi & Kita, 1998; J.Immunology. 161:4340-6). Cells were re-suspended in RPMI 1640/10% FCS solution and incubated with calcein-AM (Molecular Probes) at 37°C for 30 mins. Following incubation, the eosinophils were centrifuged at 400g for 5 min and re-suspended in RPMI/FCS at 2.2 million/ml. Cells were then incubated in the  
30 presence of increasing concentration of compounds (1 pM to 30 µM) at 37°C for 30 mins. For control responses cells were incubated with RPMI/FCS only. The agonist eotaxin (an EC<sub>80</sub> concentration) was added to the lower chamber of a 96 well chemotaxis plate (5 µm filter: Receptor Technologies). Eosinophils (50 µl of 2 million/ml cells) were added to the top chamber of the filter plate and incubated  
35 at 37°C for 45 mins. Cells remaining on top of the chemotaxis filter were removed and the number of eosinophils which had migrated were quantified by reading the plate on a fluorescent plate reader. Inhibition curves for the effect of compounds on eosinophil chemotaxis were analysed by fitting the data with a four parameter logistic equation. Functional pK<sub>i</sub> values (fpK<sub>i</sub>) were generated

using the equation below (Lazareno & Birdsall, 1995. Br.J.Pharmacol 109: 1110-9).

$$fpKi = \frac{IC_{50}}{1 + \frac{[Agonist]}{EC_{50}}}$$

5

The compounds of the Examples were tested in the CCR-3 binding and/or eosinophil chemotaxis assays (assays (a) and (b)). The compounds of the Examples tested in the CCR-3 binding assay possessed pIC<sub>50</sub> values in the range 6.6 - 9.1. The compounds of the Examples tested in the CCR-3 eosinophil  
10 chemotaxis assay possessed fpKi values such as those given in the table below:

Example No.	fpKi
34	10.3
32	9.4
78	9.3

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the  
15 respiratory tract such as bronchitis (including chronic bronchitis), bronchiectasis, asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD), cystic fibrosis, sinusitis and rhinitis. Also included are diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's  
20 disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Furthermore, compounds of the invention may be used to treat nephritis; skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions; and diseases of the central nervous system which have an  
25 inflammatory component (eg. Alzheimer's disease, meningitis, multiple sclerosis), HIV and AIDS dementia.

Compounds of the present invention may also be of use in the treatment of nasal polyposis, conjunctivitis or pruritis.

Further examples of disease states in which compounds of the invention  
30 have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome.

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

5 Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

It will be appreciated by those skilled in the art that references herein to treatment or therapy extend to prophylaxis as well as the treatment of established conditions.

10 As mentioned above, compounds of formula (I) are useful as therapeutic agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

15 There is also therefore provided a compound of formula (I), or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, e.g. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof  
20 for the manufacture of a medicament for the treatment of inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject suffering from or susceptible to an inflammatory condition e.g. asthma or rhinitis, which method comprises  
25 administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way.

There is thus further provided a pharmaceutical composition comprising a  
30 compound of formula (I), or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises admixing the compound of formula (I) or a physiologically acceptable salt or solvate thereof with one or more physiologically  
35 acceptable diluents or carriers.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional  
40 excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol,

tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, 5 croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as 10 a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan 15 mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

20 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for 25 parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multidose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory 30 agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each 35 container and freeze-drying.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents such as corticosteroids, e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide; or 40 non-steroidal anti-inflammatory drugs (NSAIDs) eg. sodium cromoglycate,



nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists; or beta adrenergic agents such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof; or antiinfective agents e.g. antibiotic agents and antiviral agents. It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, and at any appropriate frequency e.g. 1 to 4 times daily. The precise dosing regimen will of course depend on factors such as the therapeutic indication, the age and condition of the patient, and the particular route of administration chosen.

Throughout the description and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The invention is illustrated by reference to, but is in no way limited by, the following Examples.

It should be noted that, for clarity, compounds of the Descriptions and the Examples are referred to by number, for example "Description 3" and "Example 5". The structures of the compounds so referred to are given in Tables 1 and 2 for the Examples and Tables 3 and 4 for the Descriptions.

#### General experimental details

##### Mass Directed Automated Preparative HPLC column, conditions and eluent

Mass directed automated preparative high performance liquid chromatography was carried out using an LCABZ+ 5 $\mu$ m (5cm x 10mm internal diameter) column, employing gradient elution using two solvent systems, (A) 0.1% formic acid in water, and (B) 95% acetonitrile and 0.5% formic acid in water, at a flow rate of 8ml min<sup>-1</sup>. Mass spectrometry was carried out using a VG Platform Mass Spectrometer, with an HP1100 Diode Array Detector and Accurate Flow Splitter.

##### LC/MS System

The following Liquid Chromatography Mass Spectroscopy (LC/MS) System was used:

This system used an 3 $\mu$ m ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents: A – 0.1%v/v formic acid + 0.077% w/v ammonium

acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3 ml per minute. The following gradient protocol was used: 100% A for 0.7mins; A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100%B for 1.1mins; return to 100% A over 0.2mins.

- 5 The LC/MS system used a micromass spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 a.m.u.

#### Thermospray Mass Spectra

- Thermospray Mass Spectra were determined on a HP 5989A engine mass spectrometer, +ve thermospray, source temperature 250°C, probe temperatures  
10 120°C (stem), 190°C (tip), detection mass range 100-850 a.m.u. Compounds were injected in 10µl of a mixture of solvents comprising 65% methanol and 35% 0.05M aqueous ammonium acetate, at a flow rate of 0.7ml/min.

#### Solid phase extraction (ion exchange)

- 'SCX' refers to Isolute Flash SCX-2 sulphonic acid solid phase extraction  
15 cartridges.

#### Organic/Aqueous phase separation with hydrophobic frits

'Hydrophobic frit' refers to a Whatman polypropylene filter tube fitted with a PTFE frit, pore size 5.0µm.

All temperatures are in °C

20

#### Descriptions

##### Description 1: 2,2,2-Trifluoro-N-(morpholin-2-ylmethyl)acetamide

- To a stirred solution of morpholin-2-ylmethylamine (3.1g) in methanol (70ml) under nitrogen was added an ethereal solution of ethyl- $\alpha,\alpha,\alpha$ -trifluoroacetate  
25 (5ml in 20ml ether) which had been washed with saturated aqueous sodium bicarbonate, water and brine, and dried. The mixture was stirred for 30 min at 22°C before removal of all volatiles in vacuo. The residue was dissolved in methanol (10ml) and the volatiles again removed in vacuo to give the title compound as a white crunchy foam (4.9g).

- 30 Thermospray Mass Spectrum  $m/z$  213 [MH<sup>+</sup>].

##### Description 2: N-([4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl)-2,2,2-trifluoroacetamide

- To a stirred solution of Description 1 (3.3g) in N,N-dimethylformamide (50ml)  
35 under nitrogen was added potassium carbonate (2.46g) and sodium iodide (2.12g). A solution of 3,4-dichlorobenzyl chloride (2ml) in N,N-dimethylformamide (10ml) was added dropwise to the mixture. The mixture was stirred at 22°C for 18h before the volatiles were removed in vacuo. The residue was partitioned between dichloromethane (100ml) and saturated aqueous  
40 sodium carbonate solution (50ml). The organic phase was subsequently washed

with additional saturated aqueous sodium carbonate solution (2 x 50ml) and water (50ml) before drying over magnesium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 25% ethyl acetate in cyclohexane, to give the title compound as a colourless oil (2.97g).  
5 LC/MS R<sub>t</sub> 2.63 min, Mass Spectrum *m/z* 371 [MH<sup>+</sup>].

Description 3: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine

To a stirred solution of Description 2 (2.97g) in methanol (15ml) and water (5ml)  
10 was added potassium carbonate (5.53g). The mixture was stirred at 22°C for 18h before the methanol was removed in vacuo. Water (25ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). The combined organic phases were washed with water (5ml) and saturated aqueous sodium chloride solution (10ml) before drying over sodium sulphate, filtering and evaporation of  
15 the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 75:8:1 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated in vacuo to give the title compound as a colourless oil (1.85g).  
20 LC/MS R<sub>t</sub> 1.77 min, Mass Spectrum *m/z* 275 [MH<sup>+</sup>].

Description 4: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine (alternative synthesis)

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (Chem Abs No. 40172-06-3,  
25 0.980g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (1.10g) was heated at 80°C under nitrogen for 3h. The resulting solid mass was treated with concentrated sulphuric acid (1.5ml) then stirred at 150°C for 24h. The mixture was treated with water (100ml) then washed with ethyl acetate (2x100ml). The dark aqueous phase was basified to ~pH 12 using 5M aqueous sodium  
30 hydroxide, then extracted with ethyl acetate (2x100ml). The combined organic extracts were washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum to give the title compound as a brown oil (1.02g).  
Mass spec. *m/z* 275 (MH<sup>+</sup>).

35 Description 5: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine  
Description 3 (racemic mixture, 8g) was separated into its single enantiomers by preparative chiral-HPLC. The separation was carried out using a 2" x 22cm Chiralpak AD 20µm column, Merck self pack DAC system, eluting with 95:5:0.1 (v/v) heptane : absolute ethanol: diethylamine (flow rate: 55ml/min over 40min,

UV detection 225nm); sample load preparation: 400mg sample in 20ml 3:2 (v/v) absolute ethanol: system eluent.

The title compound (2.49g) was obtained as follows: preparative HPLC retention time 23.0 min.

5

Description 5 (Alternative procedure)

A slurry of Description 7 (1.00g) in water (8.5ml) was heated to 75° and then treated dropwise with concentrated sulphuric acid (2.5ml). The mixture was then heated at reflux. After 23h the reaction mixture was cooled to 22° and then  
10 treated with dichloromethane (6ml). 880 Ammonia solution (7ml) was then added dropwise with cooling. More dichloromethane (10ml) was added. The aqueous phase was separated and extracted with more dichloromethane (10ml). The combined organic phase was washed with water (5ml) and then evaporated to dryness. The residue was redissolved in dichloromethane and the solvent re-  
15 evaporated to give the product as an oil (662mg).

Description 6: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1

Description 3 (0.613g) was dissolved in methanol (12.3ml). D-Tartaric acid  
20 (0.335g) was added and the slurry was heated to reflux for 50min. The mixture was allowed to cool to 0-5°C and the precipitate isolated by filtration to give the title compound as a white solid (0.4g).

ee: 76%ee

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1

25 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Description 7: 2-[4-(3,4-Dichloro-benzyl)-morpholin-2-ylmethyl]-isoindole-1,3-dione

- A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.038 g) and (S)-2-(oxiran-2-ylmethyl)-1H-indole-1,3(2H)-dione (2.032g) in tetrahydrofuran (3.3ml) was stirred and heated at reflux under nitrogen. After 21.5h more tetrahydrofuran (12.5ml) was added and the mixture was cooled to 3°. Triphenyl phosphine (2.793g) was added and the mixture was stirred until all the solid had dissolved. Diisopropylazodicarboxylate (2.1ml) was then added over 12min maintaining the temperature at <7°. After 2.25h the mixture was allowed to warm to 22°. After 5.3h more triphenylphosphine (121mg) and diisopropylazodicarboxylate (0.09ml) were added. After 22.5h the reaction mixture was concentrated to near dryness. Propan-2-ol (12ml) was added and the concentration repeated, this was repeated once more. More propan-2-ol (12ml) was added and the mixture was heated to 70°. After 0.5h the slurry was cooled to 22° and then after a further 2h the product was collected. The bed was washed with propan-2-ol (2x4ml) and then dried in vacuo at 40° to give the product, (2.622g).

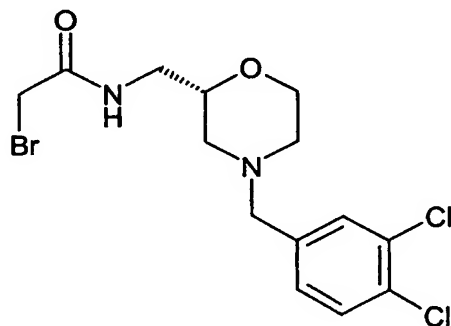
15

Description 8: [(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methanamine

Description 8 was made in an analogous manner to that of Description 5.

Preparative HPLC retention time 28.3min

- 20 Description 9: 2-Bromo-N-[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methanamide



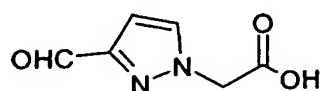
- 25 A solution of Description 5 (1.45g) in dichloromethane (25ml) was treated with bromoacetic acid (3.65g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10.1g) and the mixture stirred at room temperature for 3 hours. The solution was then washed with aqueous sodium hydrogen carbonate, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give a brown oil. Purification by chromatography on silica gel, eluting with 5% ethanol / dichloromethane, gave the title compound (1.167g) as a yellow oil.

LC-MS : Rt = 2.30min. Mass Spectrum m/z 397 [MH<sup>+</sup>]

Description 10: (3-Formyl-pyrazol-1-yl)acetic acid

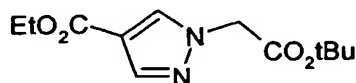
Description 10 was prepared in an analogous manner to that of Description 12.

5



Description 11: 1-tert-Butoxycarbonylmethyl-1H-pyrazole-4-carboxylic acid ethyl ester

10

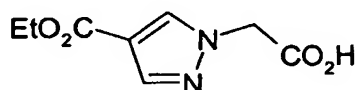


Potassium tert butoxide (0.045g) was added, in portions, to a stirred solution of 3-(ethoxycarbonyl)pyrazole [CAS 37622-90-5] (0.050g) in N,N-dimethylformamide (0.5ml). The mixture was stirred for 5 min then tert-

15 butylbromoacetate (0.078g) was added, in portions over 2 min. The mixture was stirred for 0.75h then partitioned between ethyl acetate (30ml) and 1.0M aqueous sodium bicarbonate (20ml). The organic phase was separated, washed with water (2x20ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give the title compound (0.073g) as a colourless, viscous oil.

20 LC-MS: Rt = 2.78min. Mass Spectrum m/z 255[MH<sup>+</sup>]

Description 12: 1-Carboxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester

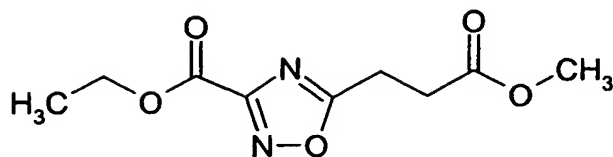


25

A solution of 4.0M hydrogen chloride in dioxan (0.5ml) was added to a stirred solution of Description 11 (0.070g) in 1,4-dioxan (3ml). The mixture was stirred for 4h. More 4.0M hydrogen chloride in dioxan (0.5ml) was added. The mixture was stirred for a further 3h then left to stand over the weekend. The solvent and  
30 excess hydrogen chloride were removed in vacuo to give the title compound (0.056g) as a pale yellow, waxy solid.

LC-MS: Rt = 1.98min. Mass Spectrum m/z 199[MH<sup>+</sup>] and 197 [MH<sup>+</sup>]

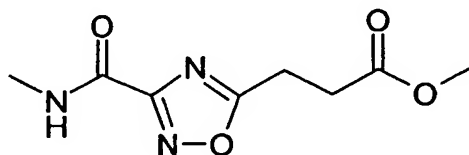
35 Description 49: 5-(2-Methoxycarbonyl-ethyl)-[1,2,4]-oxadiazole-3-carboxylic acid ethyl ester



- To succinic acid monomethyl ester (4.4g) in dry dimethoxyethane (50ml) was  
 5 added 4-dimethylamino pyridine (4.1g), amino-hydroxyimino-acetic acid ethyl  
 ester (4.4g) (for preparation see Tetrahedron, 1992, 48(30), 6335-60) and 1-[3-  
 dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (7.7g). The mixture  
 was heated to 100°C for 30 hrs then cooled and partitioned between ethyl  
 acetate and 1M aqueous hydrochloric acid. The phases were separated and the  
 10 aqueous phase extracted with more ethyl acetate. The combined organics were  
 washed with brine, dried (MgSO<sub>4</sub>) and evaporated to give a red-brown solid. The  
 solid was purified by column chromatography, eluting with 3:1 cyclohexane/ethyl  
 acetate to give the title compound as a colourless oil (1.2g), which  
 contained ~50mol% of the starting half-ester by <sup>1</sup>H NMR analysis.  
 15 <sup>1</sup>H NMR (CDCl<sub>3</sub> 400MHz) δ 4.51 (2H, q) 3.72 (3H, s) 3.30 (2H, t) 2.96 (2H, t)  
 1.45 (3H, t)

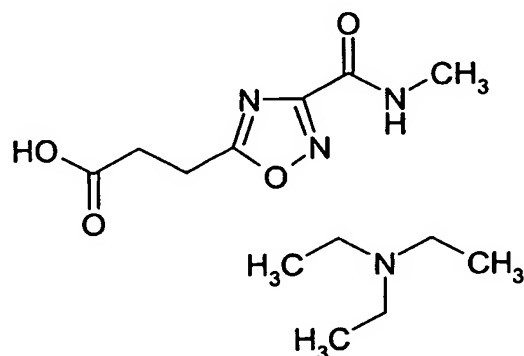
Description 54: 3-(3-Methylcarbamoyl-[1,2,4]oxadiazol-5-yl)-propionic acid  
 methyl ester

20



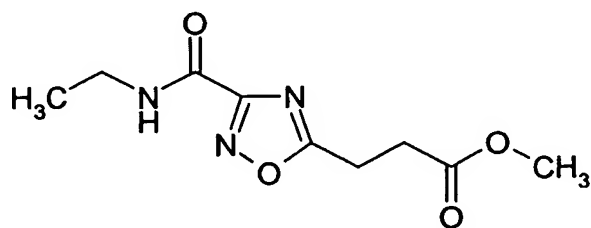
- To Description 49, the impure 5-(2-methoxycarbonyl-ethyl)-[1,2,4]-oxadiazole-3-  
 carboxylic acid ethyl ester, (0.5g) in dry methanol (5ml) was added methylamine  
 25 (2.0M in tetrahydrofuran, 10.9ml) and the mixture was stirred at room  
 temperature. After 90 mins the solvents were removed *in vacuo* to give an  
 almost white solid. The solid was purified by column chromatography, eluting  
 with 3:2 cyclohexane/ethyl acetate to give the title compound as an off-white  
 solid (0.22g).  
 30 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.93 (1H br s) 3.72 (3H, s) 3.27 (2H, t) 3.03 (3H, d) 2.94 (2H,  
 t).

Description 58: 3-(3-Methylcarbamoyl-[1,2,4]oxadiazol-5-yl)-propionic acid;  
 compound with triethylamine



To Description 54 (0.064g) in methanol (2ml) was added 2M aqueous sodium  
 5 hydroxide solution (0.30ml) and the mixture stirred at room temperature for  
 18hrs. 2M aqueous hydrochloric acid (0.30ml) was added and the mixture  
 applied directly onto a sulphonic acid ion exchange cartridge (5g, Isolute SCX,  
 pre-washed with methanol) and the cartridge eluted with methanol (x3) followed  
 by 5% triethylamine in methanol (x2). The solvent was removed from the  
 10 combined basic fractions *in vacuo* to give the title compound (0.051g).  
 LCMS  $m/z$  200  $[MH^+]$

Description 55: 3-(3-Ethylcarbamoyl-[1,2,4]oxadiazol-5-yl)-propionic acid methyl  
 ester

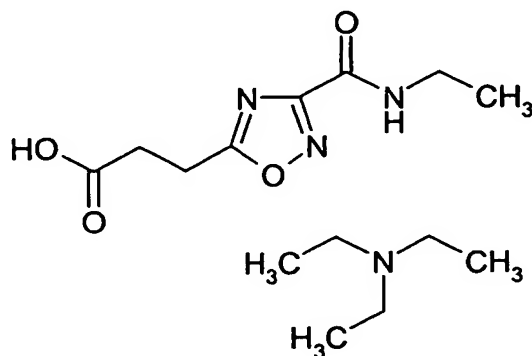


Prepared in an analogous manner to that used for Description 54 using  
 ethylamine (2M in tetrahydrofuran).  
 20  $^1H$  NMR ( $CDCl_3$ , 400MHz)  $\delta$  6.90 (1H, br s) 3.72 (3H, s) 3.52 (2H, d,q) 3.26 (2H,  
 t) 2.93 (2H, t) 2.17 (3H, t)

Description 56: 3-(3-Ethylcarbamoyl-[1,2,4]oxadiazol-5-yl)-propionic acid;  
 compound with triethylamine

25

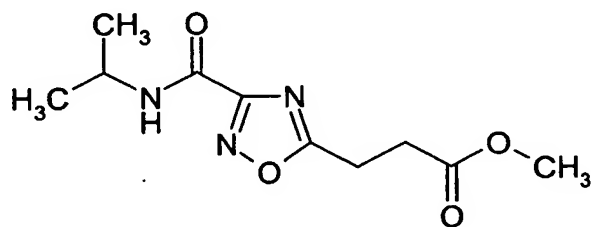




Prepared in an analogous manner to that used for Description 58 from Description 55.

5 LCMS  $m/z$  214  $[MH^+]$

Description 50: 3-(3-Isopropylcarbamoyl-[1,2,4]oxadiazol-5-yl)-propionic acid methyl ester



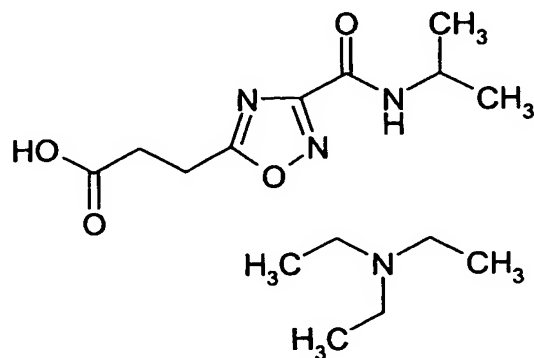
10

Prepared in an analogous manner to that used for Description 54 using isopropylamine.

$^1H$  NMR ( $CDCl_3$  400MHz)  $\delta$  6.72 (1H, br s) 4.30 (1H, m) 3.71 (3H, s) 3.25 (2H, t)

15 2.93 (2H, t) 1.27 (6H, d)

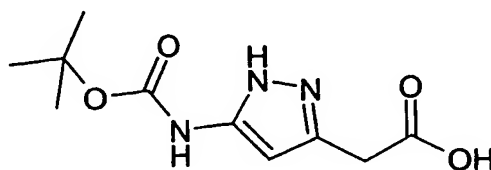
Description 57: 3-(3-Isopropylcarbamoyl-[1,2,4]oxadiazol-5-yl)-propionic acid; compound with triethylamine



Prepared in an analogous manner to that used for Description 58 from Description 50.

5 LCMS  $m/z$  228  $[MH^+]$

Description 20: (5-tert-Butoxycarbonylamino-2H-pyrazol-3-yl)acetic acid

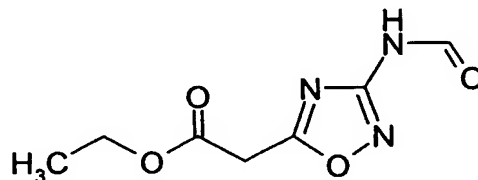


10

To a stirred solution of (5-Amino-1H-pyrazol-3-yl)acetic acid (1.0g) (for preparation see WO 95/33724) in a 10% solution of triethylamine in methanol (10ml) was added di-tert-butyl dicarbonate with vigorous stirring at room temperature under nitrogen. The mixture was heated at 50°C for 1.5h, and the  
 15 solvent evaporated *in vacuo* to give a light brown solid. Purification by Biotage™ flash chromatography on silica gel, eluting firstly with ethyl acetate:acetic acid 98:2, and then with ethyl acetate:methanol:acetic acid 88:10:2, gave, after evaporation of the solvent from the required fractions, the title compound (0.67g).  
 LCMS  $R_t$  2.21 min,  $m/z$  242  $[MH^+]$

20

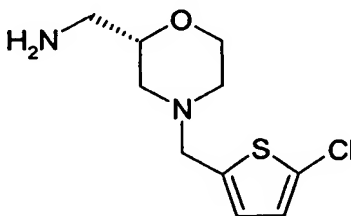
Description 14: (3-Formylamino-[1,2,4]-oxadiazol-5-yl)acetic acid ethyl ester



Formic acid (16.4ml) and acetic anhydride (38.2ml) were heated at 50°C for 30min and then cooled to room temperature. (3-Amino-[1,2,4]oxadiazol-5-yl)-acetic acid ethyl ester (5.55g) (for preparation see Tetrahedron; 1991; 47(35); 7447-7458) was added in one portion. The mixture was heated at 70°C for 5 45min, and the volatiles evaporated *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate solution, saturated aqueous brine solution, dried over magnesium sulphate, filtered and the solvent evaporated to give the title compound (6.184g) as a yellow oil which crystallised upon standing.

10

Description 18: C-[(2S)-4-(5-Chlorothiophen-2-ylmethyl)morpholin-2-yl]methylamine

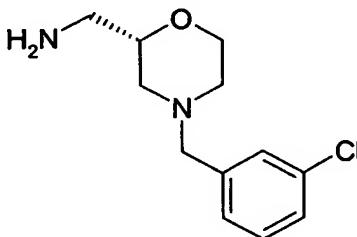


15

Description 18 was prepared in an analogous manner to that of Description 5. Chiral Preparative HPLC retention time 25.2min

Description 19: C-[(2S)-4-(3-Chlorobenzyl)morpholin-2-yl]methylamine

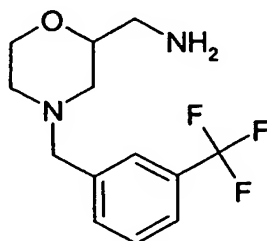
20



Description 19 was prepared in an analogous manner to that of Description 5. Preparative chiral HPLC retention time 26.1min

25

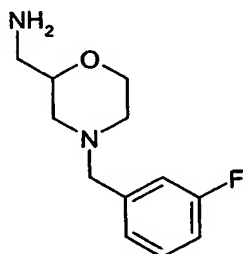
Description 16: C-[4-(3-Trifluoromethylbenzyl)morpholin-2-yl]methylamine



Description 16 was prepared in an analogous manner to that of Description 3.  
Mass spectrum observed  $m/z$  275  $[MH]^+$

5

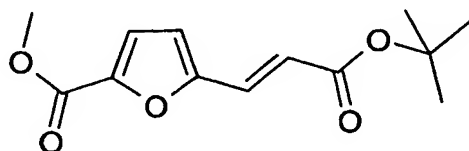
Description 17: C-[4-(3-Fluorobenzyl)morpholin-2-yl]methanamine



10 Description 17 was prepared in an analogous manner to that of Description 3.  
Thermospray Mass spectrum  $m/z$  225  $[MH]^+$

Description 25: 5-(2-tert-Butoxycarbonylvinyl)furan-2-carboxylic acid methyl ester

15



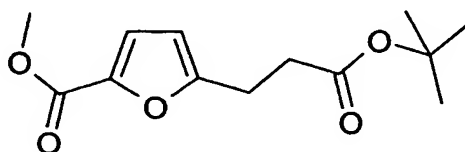
A mixture of methyl-5-bromo-2-furoate (3.6g), triphenylphosphine (0.36g), palladium acetate (0.4g), tert-butylacrylate (7.8ml) and triethylamine (27.2ml) in  
20 acetonitrile (45.4ml) was divided into 13 equal portions. Each portion was heated to 100°C for 40min in a sealed microwave vessel. Further palladium acetate (0.02g) was added to each vessel and the mixtures microwaved at 110°C for 15min. The mixtures were combined, concentrated *in vacuo*, and purified on a silica SPE cartridge. The cartridge was eluted with 10% ethyl acetate in  
25 cyclohexane. The fractions containing product were combined and concentrated *in vacuo* to give the title compound (3.2g).

LCMS R<sub>t</sub> 3.26 min, *m/z* 270 [MNH<sub>4</sub><sup>+</sup>]

Note: Microwave is a 300W Smith Creator

Description 26: 5-(2-tert-Butoxycarbonyl)ethyl)furan-2-carboxylic acid methyl ester

5

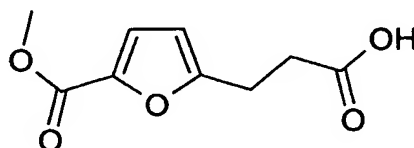


Prepared in an analogous manner to Description 29.

LCMS R<sub>t</sub> 3.10 min, *m/z* 272 [MNH<sub>4</sub><sup>+</sup>]

10

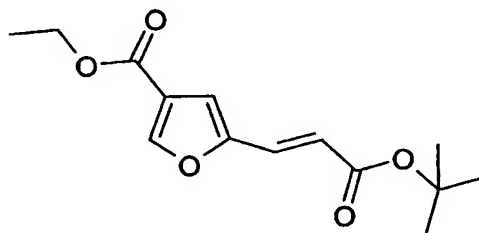
Description 27: 5-(2-Carboxyethyl)furan-2-carboxylic acid methyl ester



15 Prepared in an analogous manner to Description 28.

LCMS R<sub>t</sub> 2.17 min, *m/z* 199 [MH<sup>+</sup>]

Description 30: 5-(2-tert-Butoxycarbonylvinyl)furan-3-carboxylic acid ethyl ester



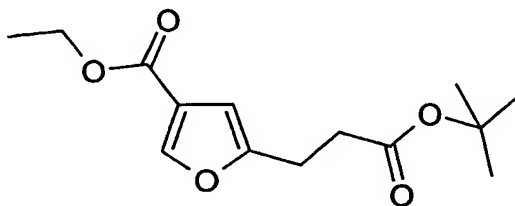
20

tert-Butyl(diethylphosphono)acetate (1.65g) in THF (5ml) was added dropwise to a suspension of 60% sodium hydride (0.262g) in THF (5ml) stirred at 0°C under nitrogen. The mixture was stirred at room temperature for 45mins then re-cooled

25 using an ice bath. A solution of ethyl 5-formylfuran 3-carboxylate (1.0g) in THF (10ml) was added dropwise to the mixture. The stirred mixture was heated to 60°C for 2hr then left at room temperature overnight. The mixture was poured into 1:1 ethyl acetate/5% aqueous sodium bicarbonate solution (100ml), was

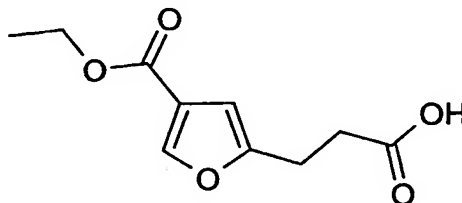
shaken, and the layers separated. The aqueous layer was extracted again with ethyl acetate (50ml) and the combined organic extracts washed with saturated aqueous brine solution (50ml), dried over magnesium sulphate, then concentrated *in vacuo*. The crude product was purified on a 50g silica SPE cartridge, eluted with 50% ethyl acetate/cyclohexane. The fractions containing product were combined and concentrated *in vacuo* to give the title compound (2.0g).  
LCMS  $R_t$  3.58min,  $m/z$  284  $[MNH_4]^+$

10 Description 29: 5-(2-tert-Butoxycarbonyl)ethyl)furan-3-carboxylic acid ethyl ester



Description 30 (1.5g) in ethanol (60ml) was added to 10% palladium on carbon catalyst (0.10g). The mixture was stirred under an atmosphere of hydrogen. After 2hrs, the catalyst was removed by filtration through Celite filter aid and the filtrate was concentrated *in vacuo*. The residue was purified on a 50g silica SPE cartridge, eluted using a solvent gradient, with initially 100% cyclohexane, then sequentially 10%, 20%, 30%, 40% and 50% dichloromethane/cyclohexane. The fractions containing product were combined and concentrated *in vacuo* to give the title compound (0.73g).  
LCMS  $R_t$  2.41min,  $m/z$  269  $[MH]^+$

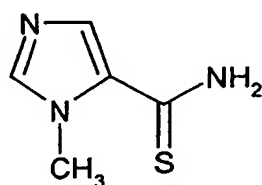
25 Description 28: 5-(2-Carboxyethyl)furan-3-carboxylic acid ethyl ester



Description 29 (0.73g) was dissolved in 1,4-dioxane (2ml), was treated with a 4M HCl in 1,4-dioxane solution (10ml) and stirred at room temperature for 6hrs. The dioxane was removed from the mixture *in vacuo* and the residue was dissolved in ethyl acetate and extracted with 5% aqueous sodium bicarbonate solution

(3x20ml). The combined aqueous extracts were acidified to pH3-4 with solid citric acid and extracted with dichloromethane (3x20ml). The combined organic extracts were washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. The residue was lyophilised from 1,4-dioxane *vacuo* to  
 5 give the title compound (0.374g).  
 LCMS R<sub>t</sub> 2.52min, *m/z* 213 [MH<sup>+</sup>]

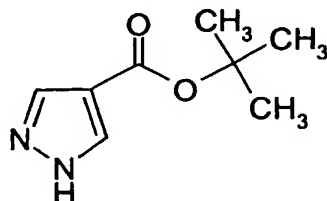
Description 15: 3-Methyl-3H-imidazole-4-carbothioic acid amide



10

To a solution of 3-methyl-3H-imidazole-4-carbonitrile (6.8g) in ethanol (100ml) was added freshly prepared ammonium polysulfide solution (102 ml) (for preparation see Journal of Organic Chemistry, 1993, 58(22), 6103-8) at room  
 15 temperature. The mixture was heated at 40°C for 6hrs and then left at room temperature overnight. The volatiles were removed from the mixture under reduced pressure to give the title compound as a brownish yellow solid (7.1g).  
 Mpt. 135-140°C.

20 Description 13: 1H-Pyrazole-4-carboxylic acid tert-butyl ester

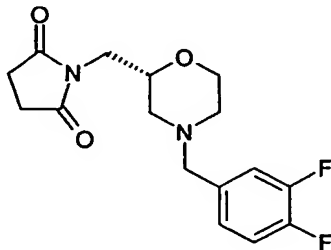


A stirred suspension of 1H-pyrazole-4-carboxylic acid (1.12g) in dry toluene  
 25 (20ml) was heated at 70°C for 15min under an atmosphere of nitrogen. To the hot suspension was added a solution of N,N-dimethylformamide-di-tert-butyl acetal (8ml) in dry toluene (8ml). The resultant solution was heated at 78°C for 21hrs. After cooling, the mixture was diluted with ethyl acetate (100ml) and washed with saturated aqueous brine solution (5x25ml). The organic phase was  
 30 dried over magnesium sulphate, filtered, and evaporated to dryness to give a gum. The gum was purified by flash column chromatography on silica gel (60g of Merck 9385) and eluted with dichloromethane/methanol 50:1. The required

fractions were combined and evaporated to dryness to give the title compound as a gum which solidified upon standing (0.481g).

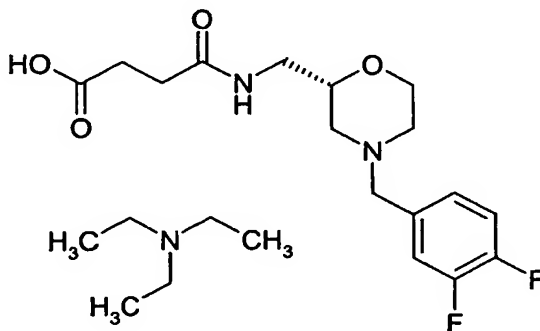
Mpt. 96-97 °C

- 5 Description 21: 1-[(2S)-4-(3,4-Difluorobenzyl)morpholin-2-ylmethyl]pyrrolidine-2,5-dione



- 10 Prepared in an analogous manner to that used for Example 27 using Description 8 and succinic acid monomethyl ester.  
LCMS  $m/z$  325 [ $MH^+$ ]

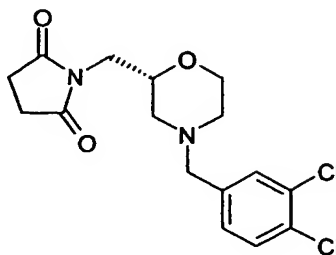
- Description 24: N-[(2S)-4-(3,4-Difluorobenzyl)morpholin-2-ylmethyl]succinamic acid  
15 acid; compound with triethylamine



- Prepared in an analogous manner to that used for Example 77 using Description 21.  
20 21.  
LCMS  $m/z$  343 [ $MH^+$ ]

- Description 22: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]pyrrolidine-2,5-dione  
25

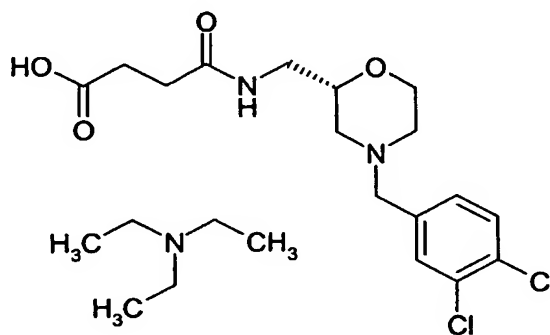




Prepared in an analogous manner to that used for Example 27 using Description 5 and succinic acid monomethyl ester.

5 LCMS  $m/z$  357  $[MH^+]$

Description 23: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]succinamic acid; compound with triethylamine



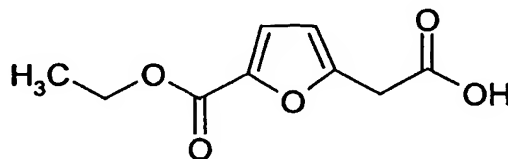
10

Prepared in an analogous manner to that used for Example 77 using Description 22.

LCMS  $m/z$  375  $[MH^+]$

15

Description 43: 5-Carboxymethylfuran-2-carboxylic acid ethyl ester

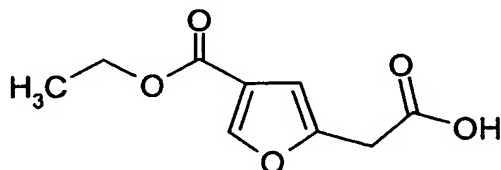


20 A mixture of ethyl 5-(chloromethyl)-2-furancarboxylate (1.0g), potassium iodide (0.0442g) and chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.261g) were stirred in formic acid (25ml). The mixture was stirred vigorously and heated at 75°C for 6hrs under an atmosphere of carbon monoxide, before cooling and allowing to

stand overnight at room temperature. The mixture was concentrated *in vacuo* to give a dark brown residue. The residue was diluted with ethyl acetate and washed with 2M aqueous hydrochloric acid (3x75ml) and saturated aqueous brine solution (2x75ml) before being dried over magnesium sulphate and filtered.

- 5 The filtrate was evaporated to dryness to give a dark green gum, which was purified Biotage™ flash chromatography on silica gel (90g cartridge) and eluted with 25% ethyl acetate and 2% acetic acid in cyclohexane. The required fractions were combined and evaporated to dryness *in vacuo* to give the title compound as a dark gum (0.672g).
- 10 LCMS  $R_f$  2.35 min,  $m/z$  199  $[MH^+]$

Description 59: 5-Carboxymethylfuran-3-carboxylic acid ethyl ester



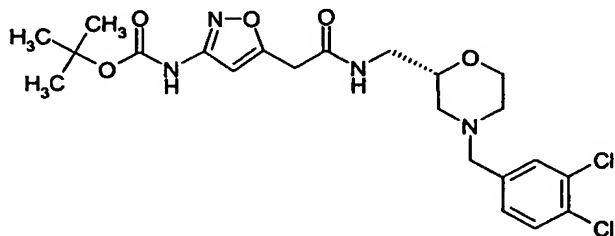
15

Prepared in an analogous manner to that used for Description 43 from 5-chloromethyl-furan-3-carboxylic acid ethyl ester (for preparation see J.Org.Chem.; 41; 1976; 2835-2846).

$^1H$  NMR ( $CDCl_3$  400MHz)  $\delta$  7.95 (1H, s) 6.63 (1H, s) 4.27 (2H, q) 3.74 (2H, s)

20 1.30 (3H, t)

Description 51: [5-({(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl}carbamoyl)methyl]isoxazol-3-yl]carbamic acid tert-butyl ester

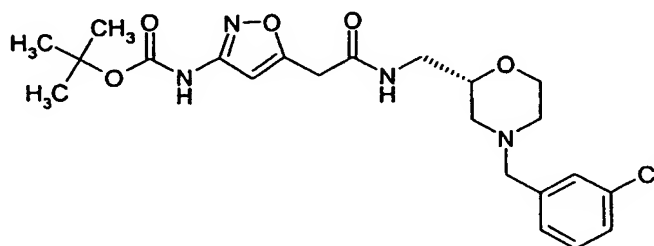


25

Prepared in an analogous manner to that used for Example 27 using (3-tert-butoxycarbonylamino-isoxazol-5-yl)acetic acid (for preparation see Tetrahedron Letters, 1996, 37(19), 3339-3342).

30 LCMS  $m/z$  499  $[MH^+]$

Description 52: [5-({[(2S)-4-(3-Chlorobenzyl)morpholin-2-ylmethyl]carbonyl}methyl)isoxazol-3-yl]carbamic acid tert-butyl ester



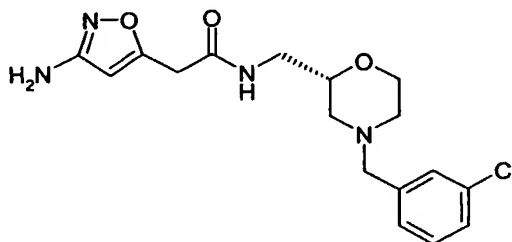
5

Prepared in an analogous manner to that used for Example 27 using Description 19 and (3-tert-butoxycarbonylamino-isoxazol-5-yl)-acetic acid (for preparation see Tetrahedron Letters, (1996), 37(19), 3339-3342).

LCMS  $m/z$  465  $[MH^+]$

10

Description 53: [2-(3-Amino-isoxazol-5-yl)-N-[(2S)-4-(3-chlorobenzyl)morpholin-2-ylmethyl]acetamide

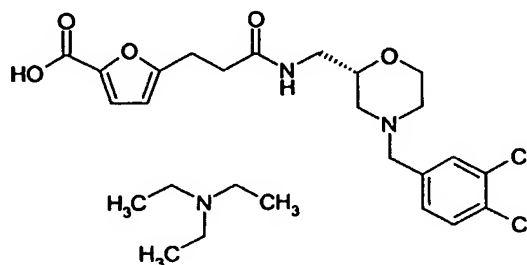


15

Prepared in an analogous manner to that used for Example 46 using Description 52.

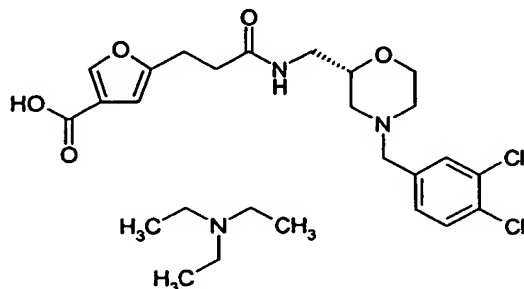
LCMS  $m/z$  365  $[MH^+]$

20 Description 44: 5-(2-({[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]carbonyl}ethyl)furan-2-carboxylic acid; compound with triethylamine



Prepared in an analogous manner to that used for Example 77 from Example 28.  
LCMS  $m/z$  441  $[MH^+]$

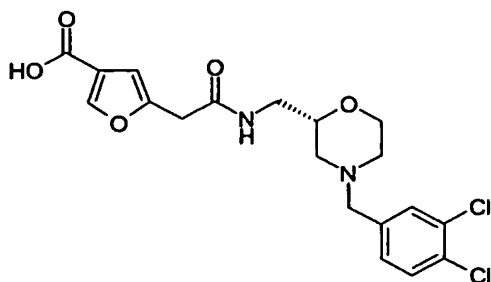
- 5 Description 45: 5-(2-(((2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]carbamoyl)ethyl)furan-3-carboxylic acid; compound with triethylamine



- 10 Prepared in an analogous manner to that used for Example 77 from Example 26.  
LCMS  $m/z$  441  $[MH^+]$

Description 46: 5-(((2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]carbamoyl)methyl)furan-3-carboxylic acid

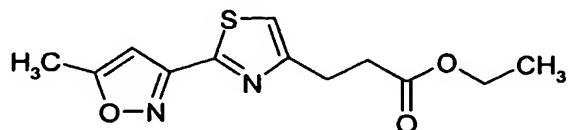
15



Prepared in an analogous manner to that used for Example 77 from Example 76.  
LCMS  $m/z$  427  $[MH^+]$

20

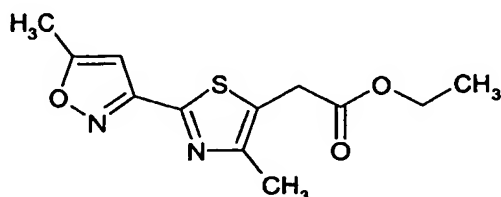
Description 47: 3-[2-(5-Methyl-isoxazol-3-yl)thiazol-4-yl]propionic acid ethyl ester with 4-oxo-pentanoic acid ethyl ester



25

- A portion (0.5ml) of a solution of bromine (5.55g) in anhydrous chloroform (4ml) was added dropwise to a solution of ethyl levulinate (5.0g) in anhydrous chloroform (30ml) at 5°C under nitrogen and the mixture was then allowed to warm to 20°C. After stirring at 20°C for 18hr, the remainder of the bromine solution was added dropwise over approximately 15 min, with the reaction temperature maintained between 10-20°C by means of a water bath. The reaction was left to stir for 7hr at 20°C and then to stand for a further 5 days at 20°C. After this time, the bromine was evaporated by bubbling nitrogen through the solution for 10min, and the mixture then evaporated *in vacuo* to give a clear light brown liquid. A portion of this liquid (1.34g) was added to 5-methyl-isoxazole-3-carbothioic acid amide (0.426g) in a 'Reactivial' along with anhydrous ethanol (1.0ml). The solution was stirred at 105°C for 3hr and then allowed to cool. The solvent was evaporated under a stream of nitrogen and the residue dissolved in dichloromethane. The solution was applied onto a silica solid phase extraction cartridge (10g, Varian Bondelut) and this was eluted sequentially with cyclohexane, followed by 5%, then 10% ethyl acetate/cyclohexane. Appropriate fractions were combined and evaporated *in vacuo* to give the title compound (0.285g) in a 1:1 ratio with ethyl levulinate as a beige solid.
- 20 LCMS R<sub>t</sub> 3.09min, *m/z* 267 [MH<sup>+</sup>]

Description 48: [4-Methyl-2-(5-methyl-isoxazol-3-yl)-thiazol-5-yl]-acetic acid ethyl ester

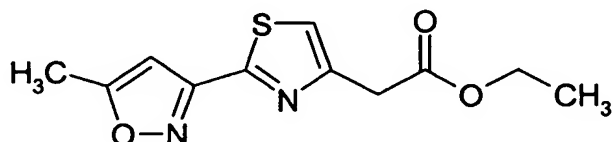


25

- A portion (0.5ml) of a solution of bromine (5.55g) in anhydrous chloroform (4ml) was added dropwise to a solution of ethyl levulinate (5.0g) in anhydrous chloroform (30ml) at 5°C under nitrogen and the mixture was then allowed to warm to 20°C. After stirring at 20°C for 18hr, the remainder of the bromine solution was added dropwise over approximately 15 min, with the reaction temperature maintained between 10-20°C by means of a water bath. The reaction was left to stir for 7hr at 20°C and then to stand for a further 5 days at 20°C. After this time, the bromine was evaporated by bubbling nitrogen through the solution for 10min, and the mixture then evaporated *in vacuo* to give a clear light brown liquid. A portion of this liquid (1.34g) was added to 5-methyl-

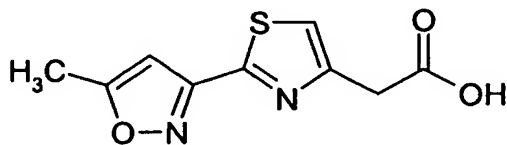
- isoxazole-3-carbothioic acid amide (0.426g) in a 'Reactivial' along with anhydrous ethanol (1.0ml). The solution was stirred at 105°C for 3hr and then allowed to cool. The solvent was evaporated under a stream of nitrogen and the residue dissolved in dichloromethane. The solution was applied onto a silica
- 5 solid phase extraction cartridge (10g, Varian Bondelut) and this was eluted sequentially with cyclohexane, followed by 5%, then 10% ethyl acetate/cyclohexane. Appropriate fractions were combined and evaporated *in vacuo* to give the title compound (0.114g) as a brown gum, as a 2:1 ratio with Description 47 as the minor component.
- 10 LCMS R<sub>t</sub> 3.06min, *m/z* 267 [MH<sup>+</sup>]

Description 31: [2-(5-Methyl-isoxazol-3-yl)thiazol-4-yl]acetic acid ethyl ester



- 15 To 5-methyl-isoxazole-3-carbothioic acid amide (0.213g) in a 'Reactivial' was added ethyl 4-chloroacetoacetate (0.305ml) and anhydrous ethanol (0.5ml). The mixture was stirred at 20°C for 16h, then at 105°C for 5h and then allowed to cool. The solvent was evaporated under a stream of nitrogen and the residue
- 20 dissolved in dichloromethane which was loaded onto a silica solid phase extraction cartridge (10g, Varian Bondelut) and this was eluted with cyclohexane and then 5% ethyl acetate/cyclohexane. Appropriate fractions were combined and evaporated *in vacuo* to give the title compound (0.252g) as a light brown solid.
- 25 LCMS R<sub>t</sub> 2.92min, *m/z* 253 [MH<sup>+</sup>]

Description 37: [2-(5-Methyl-isoxazol-3-yl)thiazol-4-yl]acetic acid

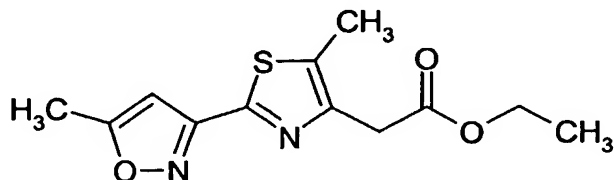


- 30 To Description 31 (0.076g) in a 'Reactivial' was added ethanol (0.665ml) and 2M aqueous sodium hydroxide solution (0.478ml) and the mixture stirred at 70°C for 3.5h. After allowing to cool, the mixture was neutralised by addition of 2M aqueous hydrochloric acid (approximately 0.375ml) then evaporated under a

stream of nitrogen to dryness to give the title compound as a mixture with inorganic salts as a brown solid.

LCMS  $R_t$  2.52 min,  $m/z$  225 [ $MH^+$ ]

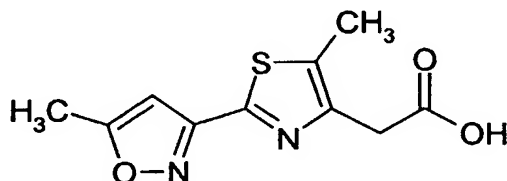
5 Description 34: [5-Methyl-2-(5-methyl-isoxazol-3-yl)thiazol-4-yl]acetic acid ethyl ester



10 Prepared in an analogous manner to that used for Description 31 using 4-bromo-3-oxo-pentanoic acid ethyl ester (for preparation see Journal of Medicinal Chemistry, 1988, 31(10), 1910-18).

LCMS  $m/z$  267 [ $MH^+$ ]

15 Description 40: [5-Methyl-2-(5-methyl-isoxazol-3-yl)thiazol-4-yl]acetic acid

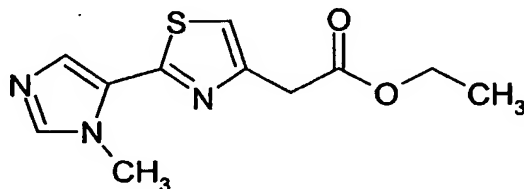


Prepared in an analogous manner to that used for Description 37 from

20 Description 34.

LCMS  $m/z$  239 [ $MH^+$ ]

Description 32: [2-(3-Methyl-3H-imidazol-4-yl)thiazol-4-yl]acetic acid ethyl ester

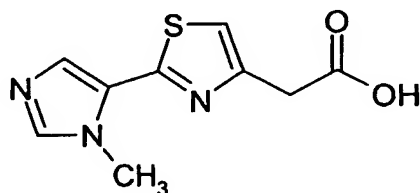


25

Prepared in an analogous manner to that used for Description 31 using Description 15.

LCMS  $m/z$  252 [ $MH^+$ ]

Description 38: [2-(3-Methyl-3H-imidazol-4-yl)thiazol-4-yl]acetic acid



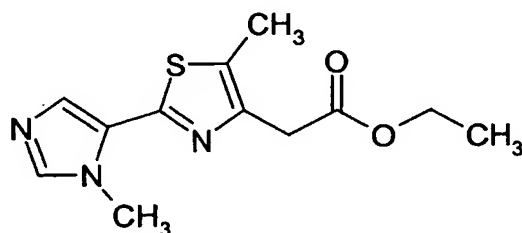
5

Prepared in an analogous manner to that used for Description 37 from Description 32.

LCMS  $m/z$  224 [ $MH^+$ ]

10

Description 35: [5-Methyl-2-(3-methyl-3H-imidazol-4-yl)thiazol-4-yl]acetic acid ethyl ester



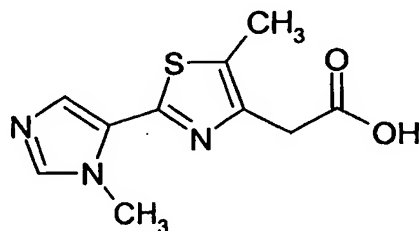
15

Prepared in an analogous manner to that used for Description 31 using Description 15 and 4-bromo-3-oxo-pentanoic acid ethyl ester (for preparation see Journal of Medicinal Chemistry, 1988, 31(10), 1910-18).

LCMS  $m/z$  266 [ $MH^+$ ]

20

Description 41: [5-Methyl-2-(3-methyl-3H-imidazol-4-yl)thiazol-4-yl]acetic acid



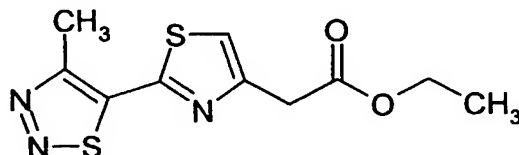
25 Prepared in an analogous manner to that used for Description 37 from Description 35.



LCMS  $m/z$  238 [MH<sup>+</sup>]

Description 33: [2-(4-Methyl-[1,2,3]-thiadiazol-5-yl)thiazol-4-yl]acetic acid ethyl ester

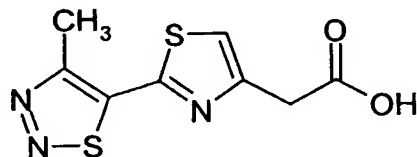
5



Prepared in an analogous manner to that used for Description 31 using 4-methyl-[1,2,3]thiadiazole-5-carbothioic acid amide (for preparation see WO 00/06606).

10 LCMS  $m/z$  270 [MH<sup>+</sup>]

Description 39: [2-(4-Methyl-[1,2,3]-thiadiazol-5-yl)thiazol-4-yl]acetic acid

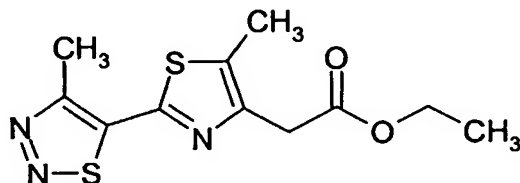


15

Prepared in an analogous manner to that used for Description 37 from Description 33.

LCMS  $m/z$  242 [MH<sup>+</sup>]

20 Description 36: [5-Methyl-2-(4-methyl-[1,2,3]-thiadiazol-5-yl)thiazol-4-yl]acetic acid ethyl ester

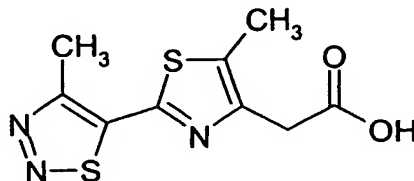


25 Prepared in an analogous manner to that used for Description 31 using 4-methyl-[1,2,3]thiadiazole-5-carbothioic acid amide (for preparation see WO 00/06606) and 4-bromo-3-oxo-pentanoic acid ethyl ester (for preparation see Journal of Medicinal Chemistry, 1988, 31(10), 1910-18).

LCMS  $m/z$  284 [MH<sup>+</sup>]

30

Description 42: [5-Methyl-2-(4-methyl-[1,2,3]-thiadiazol-5-yl)thiazol-4-yl]acetic acid



5

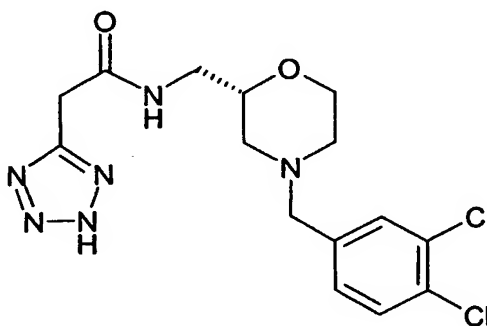
Prepared in an analogous manner to that used for Description 37 from Description 36.

LCMS  $m/z$  256  $[MH^+]$

10 Examples

Synthetic Method A

Example 10



15

A solution of 1H-tetrazole-5-acetic acid (0.172g) in N,N-dimethylformamide (2ml) was treated with 1-hydroxybenzotriazole (0.124g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.200g), Description 5 (0.176g) as a solution in N,N-dimethylformamide (1ml) and N,N-diisopropylethylamine (0.112ml), and the mixture stirred at room temperature for six days. The solution was then diluted with dichloromethane (30ml) and washed successively with saturated aqueous sodium hydrogen carbonate (30ml) and dilute aqueous sodium chloride (2 x 30ml). The organic phase was separated using three hydrophobic frits (12ml) and drained directly onto an SCX (10g) ion exchange cartridge, which had been pre-treated with methanol and which was then eluted with methanol and 10% 0.880 ammonia/methanol. The basic fractions were combined and evaporated to give a brown film which was redissolved in dichloromethane and purified by chromatography on silica gel (Varian Bond Elut, 5g), eluting successively with dichloromethane, ether, ethyl acetate, acetone, acetonitrile and methanol. The

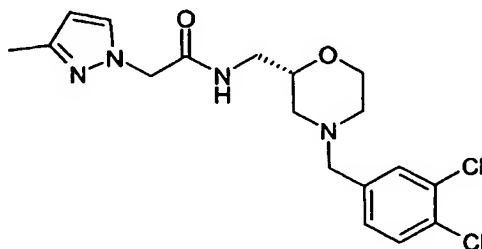
methanol fractions were combined and evaporated in vacuo to give the title compound (0.042g) as a brown gum.

LC-MS : Rt = 2.11 min. Mass Spectrum m/z 385 [MH<sup>+</sup>]

5

Synthetic Method A (alternative procedure)

Example 16



10

A solution of 3-methyl-1H-pyrazole-1-acetic acid [CAS 180741-30-4] (0.017g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.042g) in acetonitrile (2ml) was stirred for 10min then treated with a solution of Description 5 (0.030g) and N,N-diisopropylethylamine (0.045g) in acetonitrile (1ml). The mixture was stirred for 3.5h then left to stand over the weekend. The solvent was removed in vacuo. The residue was partitioned between ethyl acetate (20ml) and 0.5M aqueous sodium bicarbonate (20ml). The organic phase was separated, washed with water (20ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give the title compound (0.033g) as a pale brown gum.

15

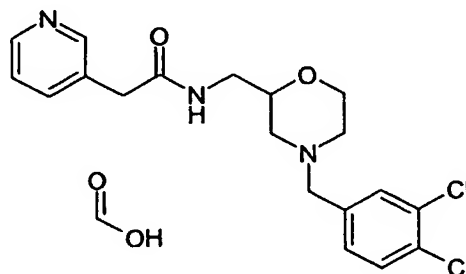
20

LC-MS: Rt = 2.18min. Mass Spectrum m/z 397[MH<sup>+</sup>]

Synthetic Method A (Alternative Procedure 2)

Example 33: N-[4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]2-pyridin-3-yl-

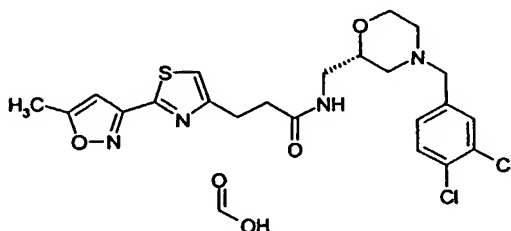
25 acetamide; compound with formic acid



To pyridin-3-yl-acetic acid (0.027g) was added a portion (0.25ml) of a solution of Description 3 (0.955g) in dichloromethane (3.72ml) and the dichloromethane allowed to evaporate. The mixture was had N-methylpyrrolidinone (1 drop) added to it before being subjected to heating in a microwave oven (4 minutes at full power) then allowed to cool. The sample was purified by mass-directed preparative HPLC and the solvent removed *in vacuo* to give the title compound (0.018g).  
LCMS R<sub>t</sub> 2.03min, *m/z* 394 [MH<sup>+</sup>]

10 Synthetic Method A (Alternative Procedure 3)

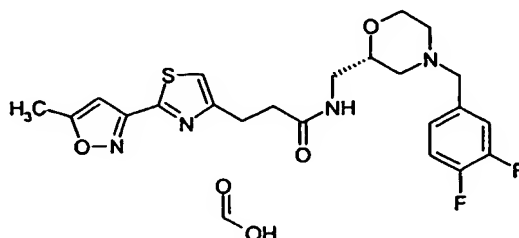
Example 84: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-3-[2-(5-methyl-isoxazol-3-yl)thiazol-4-yl]propionamide; compound with formic acid



15

To Description 47 (0.073g) in a 'Reactivial' was added ethanol (0.665ml) and 2M aqueous sodium hydroxide solution (0.478ml) and the mixture stirred at 70°C for 3.5hr. After allowing to cool, the mixture was neutralised by addition of 2M aqueous hydrochloric acid (approximately 0.375ml) then the solvents evaporated to dryness under a stream of nitrogen to leave a beige solid. Half of the solid was added to Description 5 (0.039g), in N,N-dimethylformamide (1ml) followed by 1-hydroxybenzotriazole (0.027g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.044g) and N,N-diisopropylethylamine (0.027ml). The mixture was stirred at 20°C for 19hr, then diluted with dichloromethane (7.5ml). The mixture was washed successively with dilute aqueous sodium hydrogen carbonate solution (7.5ml) and dilute aqueous sodium hydroxide solution (2x7.5ml) with vigorous shaking. The organic phase was separated using a hydrophobic frit and applied directly onto a sulphonic acid ion exchange cartridge (2g, Isolute SCX, pretreated with methanol). Four column volumes of methanol were eluted and discarded. Two column volumes of 10% 0.880 ammonia/methanol was eluted, collected and evaporated to dryness under a stream of nitrogen to give a brown gum. The gum was further purified by mass-directed preparative HPLC to give, after evaporation of the solvents under a stream of nitrogen, the title compound (0.008g) as a colourless film.  
LCMS R<sub>t</sub> 2.83 min, *m/z* 495 [MH<sup>+</sup>]

Example 86: N-[(2S)-4-(3,4-Difluorobenzyl)morpholin-2-ylmethyl]-3-[2-(5-methylisoxazol-3-yl)thiazol-4-yl]propionamide; compound with formic acid



5

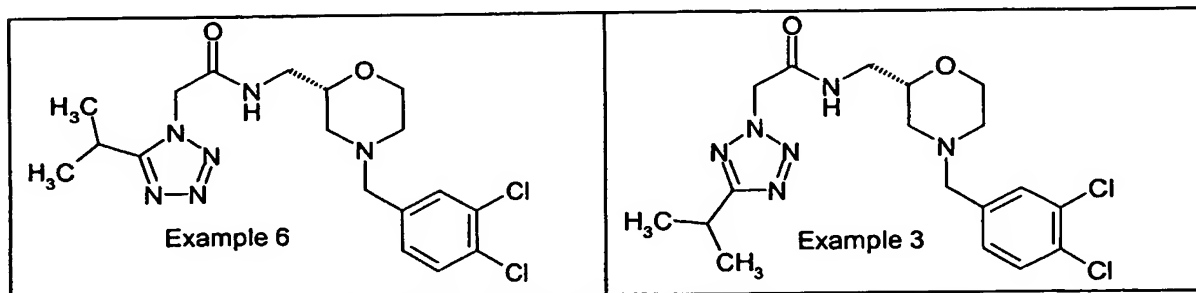
Prepared in an analogous manner to that used for Example 84 using Description 8.

LCMS R<sub>t</sub> 2.59 min, *m/z* 463 [MH<sup>+</sup>]

10

Synthetic Method B

Example 6 and Example 3



A solution of 5-isopropyltetrazole (Tetrahedron (1999), 55(29), 8997-9006)

- 15 (0.095g) in N,N-dimethylformamide (10ml) was treated with lithium bis(trimethylsilyl)amide (0.155g) and stirred at room temperature for twenty five minutes. Description 9 (0.167g) was then added as a solution in N,N-dimethylformamide (10ml) and the mixture stirred at 60° for 16 hours. After cooling, the solvent was removed, the residue was dissolved in dichloromethane
- 20 and this solution washed with water. The aqueous phase was extracted with dichloromethane, then the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent concentrated under vacuum to give a residue which was purified using mass directed HPLC. Appropriate fractions were combined and evaporated to give the title compound Example 6 (0.021g) as a colourless oil.
- 25 LC-MS : R<sub>t</sub> = 2.21min. Mass Spectrum *m/z* [MH<sup>+</sup>] 427

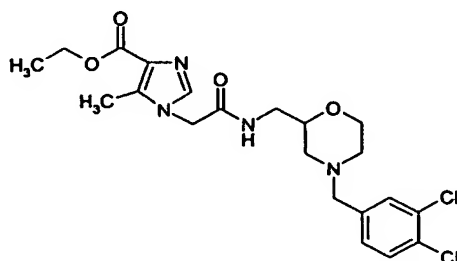
Appropriate other fractions were combined and evaporated to give the title compound Example 3 (0.027g) as a colourless oil.

LC-MS : Rt = 2.35min. Mass Spectrum m/z [MH<sup>+</sup>] 427

Synthetic Method B (Alternative procedure 1)

Example 37: 1-({[4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]carbonyl}methyl)-

5 5-methyl-1H-imidazole-4-carboxylic acid ethyl ester



3,5-Dimethyl-4-formyl phenoxyethoxymethyl polystyrene aldehyde resin (1.0g @  
 10 0.9mmol/g loading) was swollen with the minimum quantity of a solution of 1% acetic acid in N,N-dimethylformamide to form a slurry. A solution of Description 3 (0.969g) in N,N-dimethylformamide (2ml) was added and the mixture shaken at room temperature for 100 min. A solution of 1% acetic acid in N,N-dimethylformamide (10ml) was added, followed by sodium triacetoxymethylborohydride  
 15 (0.333g). The reaction was shaken for 20 min before a further portion of sodium triacetoxymethylborohydride (0.30g) was added and the reaction shaken at room temperature for a further 18 hrs. The reaction solution was removed by filtration and the resin washed with N,N-dimethylformamide (5 x 10ml), methanol (5 x 10ml), dichloromethane (5 x 10ml) and diethyl ether (3 x 10ml) before being dried  
 20 *in vacuo*. A portion of the resin (0.10g) was swollen with dichloromethane and then drained. A solution of diisopropylcarbodiimide (0.0705ml) and bromo acetic acid (0.125g) in a 1:1 solution of dichloromethane/N,N-dimethylformamide (1ml) was prepared and stirred for 5 min before being added to the resin. The resin mixture was shaken at room temperature for 2 hrs, the reaction solution removed  
 25 by filtration and the resin washed with N,N-dimethylformamide (5 x 10ml), methanol (5 x 10ml) and dichloromethane (5 x 10ml). A solution of potassium-*tert*-butoxide (50mg) and 4-bromo-1H-imidazole (0.132g) in N,N-dimethylformamide (1ml) was prepared and stirred for 5 min before this was added to the resin. The reaction mixture was heated to 60°C and shaken for 18  
 30 hrs. The reaction solution was removed by filtration and the resin washed with N,N-dimethylformamide (5 x 1ml), methanol (5 x 1ml) and dichloromethane (5 x 1ml). A 1:1 solution of trifluoroacetic acid/dichloromethane (1ml) was added to the resin. The mixture was shaken for 90 min, before the reaction solution was collected by filtration. This was combined with the solution from washing the

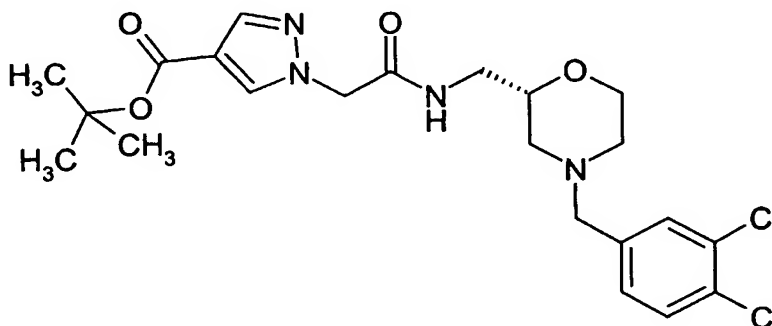
resin with dichloromethane (1ml). The volatiles were removed by evaporation and the residue was purified by mass-directed-autoprep to give the title compound (0.008g).

LCMS  $R_t$  2.33 min,  $m/z$  469  $[MH^+]$ .

5

Synthetic Method B Alternative procedure 2

Example 45: 1-(((2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl)carbamoyl)methyl)-1H-pyrazole-4-carboxylic acid tert-butyl ester



10

Potassium tert-butoxide (0.045g) was added to a solution 1H-pyrazole-4-carboxylic acid tert-butyl ester (0.055g) in N,N-dimethylformamide (1ml). The mixture was stirred at 20°C for 0.75h before a solution of Description 9 (0.099g)

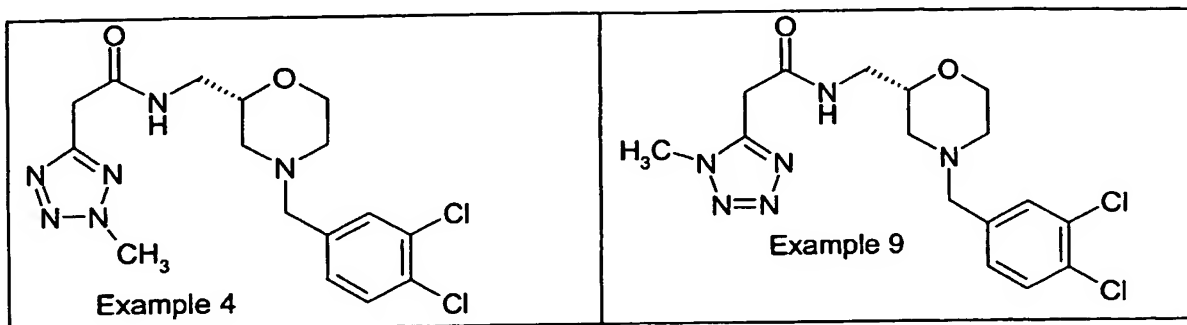
15 in N,N-dimethylformamide (0.5ml) was added to it. The mixture was stirred at 20°C for 2h then left to stand overnight. The mixture was diluted with ethyl acetate (35ml), washed with 1M aqueous sodium bicarbonate solution (30ml) and water (30ml), dried over sodium sulphate and concentrated *in vacuo* to give a gum. The gum was purified on a 20g SPE cartridge, eluting initially with ethyl acetate and then with a (100:1) mixture of ethyl acetate/methanol. The product

20 containing fractions were evaporated *in vacuo* to give the title compound (0.032g) as a pale brown gum.

LCMS  $R_t$  2.62 min,  $m/z$  483  $[MH^+]$

25 Synthetic Method C (interconversion)

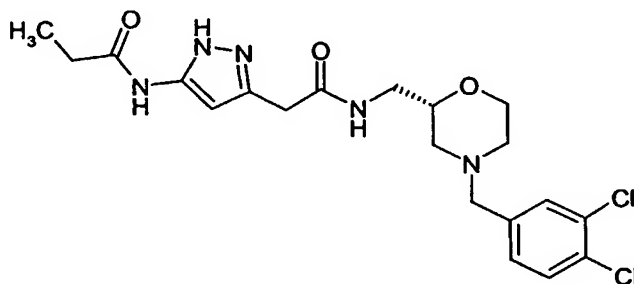
Example 4 and Example 9



- A stirred solution of Example 10 (0.038g) in dichloromethane (1.5ml) and methanol (0.5ml) was treated dropwise at room temperature with (trimethylsilyl)diazomethane (0.22ml of 10% solution in hexane). After 2 hours stirring at room temperature, acetic acid (0.1ml) was added and the solvent evaporated under a stream of nitrogen to dryness. The residue was loaded onto an SCX (2g) ion exchange cartridge, which had been pre-treated with methanol and which was then eluted with methanol and 10% 0.880 ammonia/methanol. The basic fractions were combined and evaporated and the residue was purified by chromatography on silica gel (Varian Bond Elut, 2g), eluting with 5% methanol/ethyl acetate then methanol. Mixed fractions were repurified similarly on silica gel (Varian Bond-Elut, 1g) to give the title compound Example 4 (0.0073g) as a clear colourless film. LC-MS : Rt = 2.14 min. Mass Spectrum m/z 399 [MH<sup>+</sup>]
- Other appropriate fractions were combined and evaporated to give the title compound Example 9 (0.0061g) as a clear colourless film. LC-MS : Rt = 2.14 min. Mass Spectrum m/z 399 [MH<sup>+</sup>]

20 Synthetic Method D (Interconversion)

Example 63: N-[5-(((2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl)carbamoyl)methyl]-2H-pyrazol-3-yl]propionamide

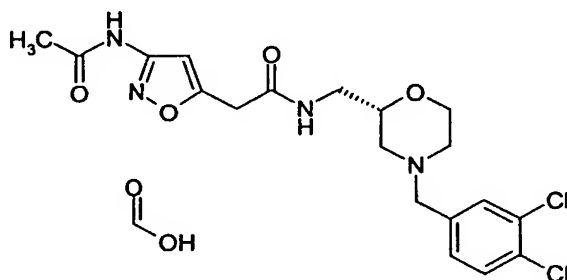




To Example 59 (0.036g) in N,N-dimethylformamide (1ml) was added N,N-diisopropylethylamine (0.035ml) and propanoyl chloride (0.0086ml), and the mixture was stirred at 20°C for 5h. The mixture was applied directly to a sulphonic acid ion exchange cartridge (1g, Isolute SCX), and eluted with  
 5 methanol followed by 10% 880 ammonia in methanol. The methanol/ammonia fraction was evaporated to give the crude product. Purification by mass-directed preparative HPLC gave the title compound (0.0061g).  
 LCMS  $R_t$  2.16 min,  $m/z$  454 [ $MH^+$ ]

#### 10 Synthetic Method E (Interconversion)

Example 100: 2-(3-Acetylamino-isoxazol-5-yl)-N-[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-ylmethyl]acetamide; compound with formic acid

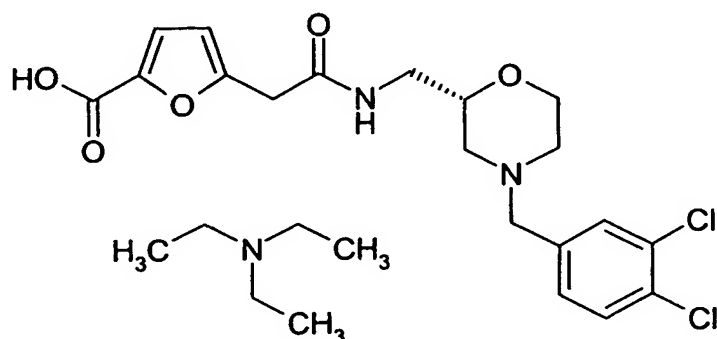


15 To a solution of Example 98 (0.050g) in anhydrous dichloromethane (3.5ml) was added N,N-diisopropylethylamine (0.033ml) and acetyl chloride (0.0135ml). After stirring for 3hrs at 20°C, further N,N-diisopropylethylamine (0.022ml) and acetyl chloride (0.009ml) were added. The mixture was stirred at 20°C overnight before the solvent was removed under a stream of nitrogen. The residue was diluted  
 20 with ethanol (4ml) and had 0.880 ammonia (0.1ml) added to it before stirring at 20°C for 20mins. The solvent was partially removed under a stream of nitrogen and the mixture was applied directly to a sulphonic acid ion exchange cartridge (2g, Isolute SCX, pretreated with methanol) and the cartridge eluted with methanol followed by 5% triethylamine in methanol. The solvent was removed  
 25 from the basic fraction *in vacuo* and the residue purified by mass-directed preparative HPLC to give, after removal of the solvent, the title compound (0.0197g).

LCMS  $R_t$  2.19 min,  $m/z$  441 [ $MH^+$ ]

#### 30 Synthetic Method F (Interconversion)

Example 77: 5-([(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]carbamoyl)methyl)furan-2-carboxylic acid; compound with triethyl-amine

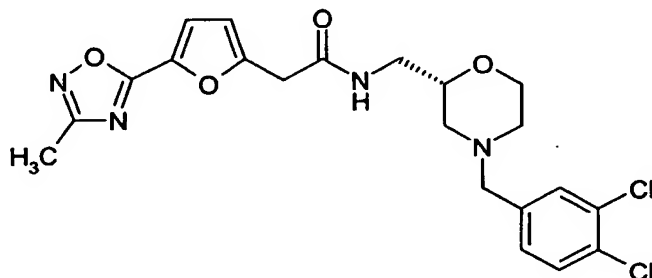


- To a solution of Example 75 (0.222g) in methanol (3ml) was added 2M aqueous sodium hydroxide solution (0.488ml) and water (3ml). The mixture was stirred at 20°C for 0.5h before being left to stand overnight. The mixture was concentrated *in vacuo* to give a gum, which was re-dissolved in water and the pH of the solution was adjusted to pH7 by the addition of 2M aqueous hydrochloric acid. The mixture was applied onto a sulphonic acid ion exchange cartridge (10g, Isolute SCX, pretreated with methanol) and the cartridge was eluted with water (x3) followed by 5% triethylamine in methanol (x2). The solvent was removed from the first basic fraction *in vacuo*. The residue was dissolved in acetonitrile and the solvent removed under a stream of nitrogen to give the title compound as a light brown gum (0.223g).
- LCMS  $R_t$  2.21 min,  $m/z$  427  $[MH^+]$

#### Synthetic Method G (Interconversion)

Example 50: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-2-[5-(3-methyl-[1,2,4]oxadiazol-5-yl)furan-2-yl]acetamide

20



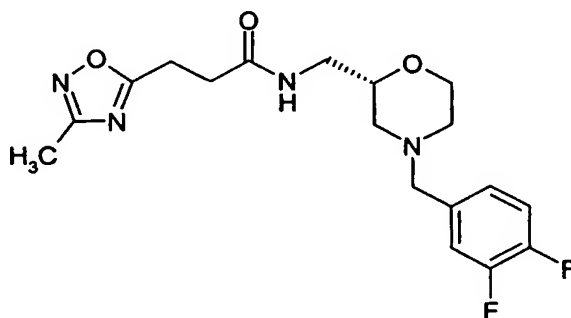
- To a solution of Example 75 (0.0642g) in ethanol (2ml) was added acetamidoxime (0.052g) (prepared according to Journal of Medicinal Chemistry (1986), 29(11), 2174-83) in ethanol (2ml). The suspension was treated with activated 4A powdered molecular sieves (0.240g) and stirred for 5mins. To the

suspension was added 21% sodium ethoxide in ethanol (0.104ml) and the mixture heated at reflux for 4.75hrs. The mixture was cooled and allowed to stand overnight at room temperature. The mixture was applied directly onto a sulphonic acid ion exchange cartridge (5g, Isolute SCX, pretreated with methanol) and the cartridge was eluted with methanol (x3) followed by 10% 0.880 ammonia in methanol (x2). The solvent was removed from the first basic fraction *in vacuo*. The residue was re-dissolved in acetonitrile/methanol and was applied directly onto a quaternary ammonium ion exchange cartridge (5g, Isolute SAX, pretreated with acetonitrile) and the cartridge was eluted with acetonitrile (x3) followed by 10% citric acid in acetonitrile (x2). The solvent was removed from the first acetonitrile fraction *in vacuo*. The residue was further purified by mass-directed preparative HPLC to give, after removal of the solvent *in vacuo*, the title compound as a colourless glass (0.0032g).  
LCMS R<sub>t</sub> 2.46 min, *m/z* 465 [MH<sup>+</sup>]

15

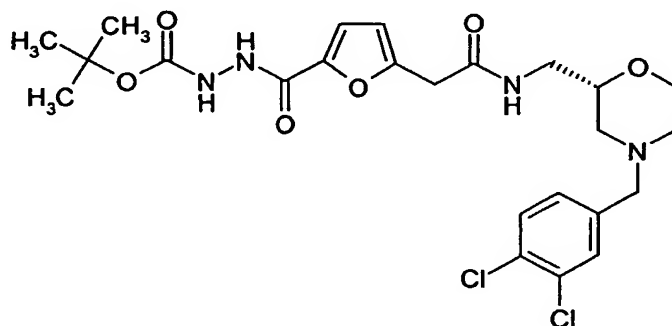
#### Synthetic Method H

Example 69: N-[(2S)-4-(3,4-Difluorobenzyl)morpholin-2-ylmethyl]-3-(3-methyl-[1,2,4]oxadiazol-5-yl)propionamide



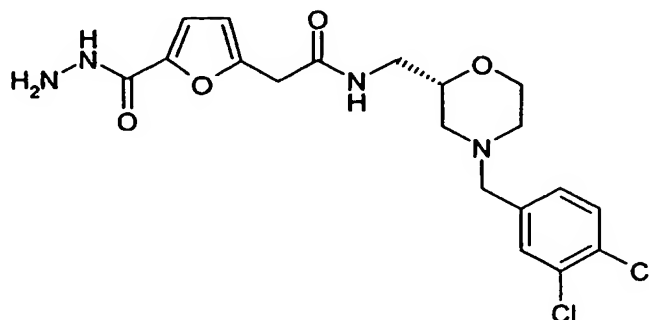
20

A mixture of Description 24 (0.055g), 4-(N,N-dimethyl)aminopyridine (0.010g), methylamidoxime (0.015g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.027g) in 1,2-dimethoxyethane (2ml) was heated at 100°C for 3 days. After cooling, the mixture was applied directly onto a sulphonic acid ion exchange cartridge (5g, Isolute SCX, pretreated with methanol) and the cartridge was eluted with methanol (x3) followed by 10% 0.880 ammonia in methanol (x2). The solvent was removed from the first basic fraction *in vacuo*. The residue was further purified by Biotage™ flash chromatography on silica gel (8g cartridge), eluting with 100:8:1 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated *in vacuo* to give the title compound as a pale yellow gum (0.0194g).  
LCMS R<sub>t</sub> 1.86 min, *m/z* 381 [MH<sup>+</sup>]

Synthetic Method I (Interconversion)Example 30: N'-[5-(((2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]carbamoyl)methyl)furan-2-carbonyl]hydrazinecarboxylic acid tert-butyl5 ester

To a solution of Example 77 (0.084g) in N,N-dimethylformamide (3ml) was added  
 10 1-hydroxybenzotriazole (0.030g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0525g). The mixture was stirred at 20°C for 10mins before tert-butylcarbazide (0.0226g) and N,N-diisopropylethylamine (0.0596ml) were added and the mixture stirred for a further 30mins at 20°C before being left to stand overnight. The mixture was diluted with methanol and  
 15 applied directly onto a sulphonic acid ion exchange cartridge (5g, Isolute SCX, pretreated with methanol) and the cartridge was eluted with methanol (x3) followed by 10% 0.880 ammonia in methanol (x2). The solvent was removed from the first basic fraction *in vacuo*. The residue was further purified by Biotage™ flash chromatography on silica gel (8g cartridge), eluting with 170:8:1  
 20 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated *in vacuo* to give the title compound as a white solid (0.0655g).

LCMS R<sub>t</sub> 2.47 min, m/z 541 [MH<sup>+</sup>]25 Synthetic Method J (Interconversion)Example 46: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-2-(5-hydrazinocarbonylfuran-2-yl)acetamide

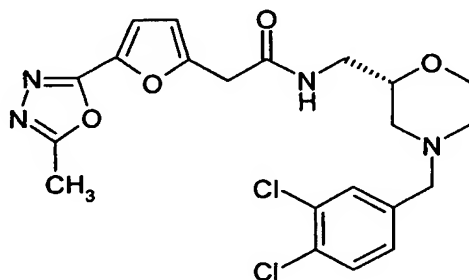


To a solution of Example 30 (0.0655g) in methanol (4ml) was added 4.0M HCl in 1,4-dioxane (1ml) and the mixture was stirred at 20°C for 3hrs. The volatiles  
 5 were removed *in vacuo* and the residue re-dissolved in methanol and applied directly onto a sulphonic acid ion exchange cartridge (5g, Isolute SCX, pretreated with methanol). The cartridge was eluted with methanol (x3) followed by 10% 0.880 ammonia in methanol (x2). The solvent was removed from the first basic fraction *in vacuo* to give the title compound as a colourless glass (0.0532g).  
 10 LCMS  $R_t$  2.05 min,  $m/z$  441 [ $MH^+$ ]

#### Synthetic Method K (Interconversion)

Example 48: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-2-[5-(5-methyl-[1,3,4]oxadiazol-2-yl)furan-2-yl]acetamide

15

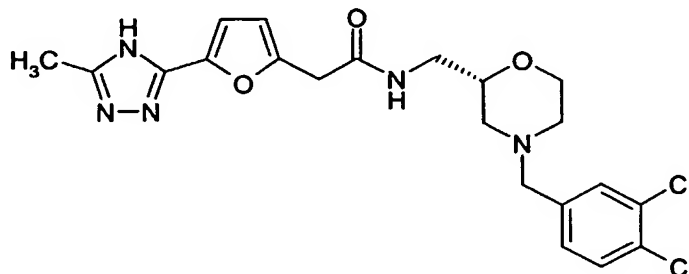


A solution of Example 46 (0.0312g) in triethylorthoacetate (0.22ml) was heated in a 'Reacti-vial' at 160°C for 21hrs. The mixture was diluted with methanol and  
 20 directly applied onto a sulphonic acid ion exchange cartridge (5g Isolute SCX, pre-washed with methanol). The cartridge was eluted with methanol followed by 10% 0.880 ammonia in methanol and the first basic fraction concentrated *in vacuo*. The residue was further purified by mass-directed preparative HPLC to give, after removal of the solvent *in vacuo*, the title compound as a colourless  
 25 gum (0.0117g).  
 LCMS  $R_t$  2.41 min,  $m/z$  465 [ $MH^+$ ]

Synthetic Method L (Interconversion)

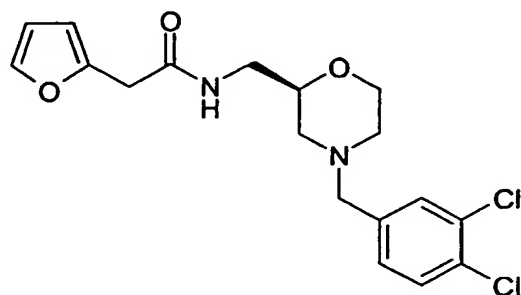
Example 78: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-2-[5-(5-methyl-4H-[1,2,4]triazol-3-yl)furan-2-yl]acetamide

5



- A solution of sodium hydroxide (0.102g) in anhydrous methanol (3ml) was prepared and a portion of the solution (0.142ml) added to ethyl acetimidate hydrochloride (0.015g). After stirring the mixture for 2min and leaving to stand for a further 5min, the supernatant of the mixture was transferred by syringe to a 'Reacti-vial' charged with Example 46 (0.0532g). The mixture was heated to 90°C for 3hrs before cooling to room temperature and concentrating under a stream of nitrogen. The concentrated mixture was purified by mass-directed preparative HPLC and the solvent removed *in vacuo* to give a colourless gum. The gum was further purified by dissolving in dichloromethane and applying the solution to a silica solid phase extraction cartridge (0.5g, Varian Bondelut, pre-washed with dichloromethane) eluting sequentially with dichloromethane, chloroform, ether, ethyl acetate, acetonitrile, acetone and methanol. The solvent was evaporated from the acetone fractions *in vacuo* and the residue further purified by Biotage™ flash chromatography on silica gel (8g cartridge), eluting with 100:8:1 dichloromethane/ethanol/0.880 ammonia solution. The solvents were evaporated from the required combined fractions to give the title compound as a colourless gum (0.0051g).
- LCMS  $R_t$  2.32 min,  $m/z$  464 [ $MH^+$ ]

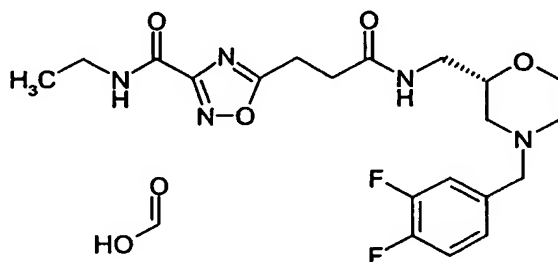
Example 35: N-[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-2-furan-2-yl-acetamide



The racemic mixture (0.018g) (for preparation see WO 02/26722) was separated on a Chiralpak AD preparative hplc column (25x2cm), eluted with 20% ethanol in n-heptane. The flow rate was 10ml/min and detection wavelength 215nm. Fractions containing the required product (first eluting enantiomer) were combined and evaporated. The residue obtained was re-dissolved in 1,4-dioxane and lyophilised to give the title compound (0.013g). LCMS  $R_t$  2.46 min,  $m/z$  383  $[MH^+]$

10

Example 27: 5-(2-([(2S)-4-(3,4-Difluorobenzyl)morpholin-2-ylmethyl]carbamoyl)ethyl)-[1,2,4]oxadiazole-3-carboxylic acid ethylamide; compound with formic acid



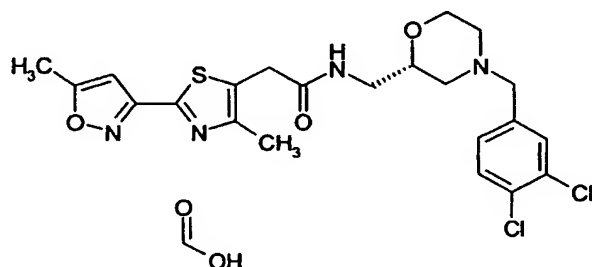
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To a solution of Description 8 (0.016g) in anhydrous N,N-dimethylformamide (2ml) was added Description 56 (0.0275g). To the solution was added 1-hydroxybenzotriazole (0.0107g), N,N-diisopropylethylamine (0.024ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.015g). The mixture was stirred at 20°C for 17h. The mixture was applied onto a sulphonic acid ion exchange cartridge (2g, Isolute SCX, pretreated with methanol) and the cartridge eluted with methanol followed by 10% 0.880 ammonia in methanol. The solvent was removed from the basic fraction *in vacuo*. The residue was purified by mass-directed preparative HPLC to give, after removal of the solvent, the title compound (0.0063g). LCMS  $R_t$  2.02 min,  $m/z$  438  $[MH^+]$

20

25

Example 88: N-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-ylmethyl]-2-[4-methyl-2-(5-methyl-isoxazol-3-yl)thiazol-5-yl]acetamide; compound with formic acid



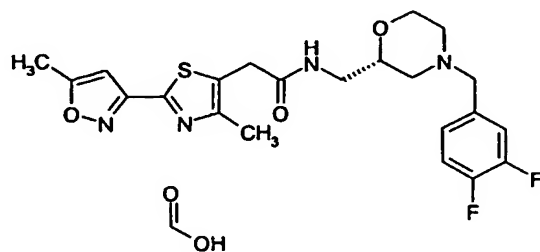
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- To Description 48 (0.071g) in a 'Reactivial' was added ethanol (0.665ml) and 2M aqueous sodium hydroxide solution (0.478ml) and the mixture stirred at 70°C for 3.5hr. After allowing to cool, the mixture was neutralised by addition of 2M aqueous hydrochloric acid (approximately 0.375ml) then evaporated under a stream of nitrogen to leave a brown solid. Half of the solid was added to Description 5 (0.039g), in N,N-dimethylformamide (1ml) followed by 1-hydroxybenzotriazole (0.027g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.044g) and N,N-diisopropylethylamine (0.027ml). The mixture was stirred at 20°C for 19h then diluted with dichloromethane (7.5ml). The solution was washed successively with dilute aqueous sodium hydrogen carbonate solution (1x7.5ml) and dilute aqueous sodium hydroxide solution (2x7.5ml) with vigorous shaking. The organic phase was separated using a hydrophobic frit and applied directly onto a sulphonic acid ion exchange cartridge (2g, Isolute SCX, pretreated with methanol). Four column volumes of methanol were eluted and discarded. Two column volumes of 10% 0.880 ammonia/methanol was eluted, collected and evaporated to dryness under a stream of nitrogen to give a brown gum. The gum was further purified by mass-directed preparative HPLC to give, after evaporation of the solvents under a stream of nitrogen, the title compound (0.008g) as a clear brown film as a 3:1 mixture with Example 84 as the minor component.
- LCMS R<sub>t</sub> 2.82 min, m/z 495 [MH<sup>+</sup>]

Example 90: N-[(2S)-4-(3,4-Difluorobenzyl)morpholin-2-ylmethyl]-2-[4-methyl-2-(5-methyl-isoxazol-3-yl)thiazol-5-yl]acetamide; compound with formic acid

30

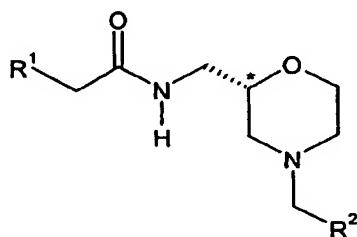




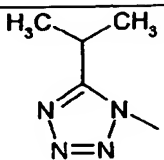
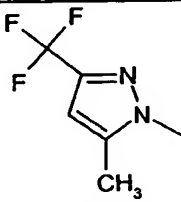
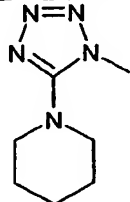
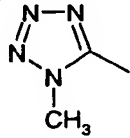
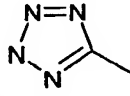
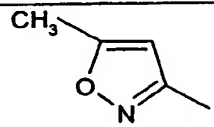
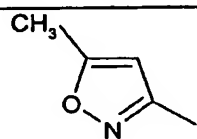
Prepared in an analogous manner to that used for Example 88 using Description 8.

5 LCMS  $R_t$  2.57 min,  $m/z$  463  $[MH^+]$

Table 1



Ex. No.	Synthetic Method	R <sup>1</sup>	R <sup>2</sup>	Stereochem at position (*)	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) [M+H] <sup>+</sup> of lowest mass isomer unless otherwise indicated
1	B		3,4-di-ClPh	S	466.393	466
2	B		3,4-di-ClPh	S	468.39	468
3	B		3,4-di-ClPh	S	427.337	427
4	A+C		3,4-di-ClPh	S	399.283	399
5	B		3,4-di-FPh	S	446.523	447

Ex. No.	Synthetic Method	R <sup>1</sup>	R <sup>2</sup>	Stereochem at position (*)	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) [M+H] <sup>+</sup> of lowest mass isomer unless otherwise indicated
6	B		3,4-di-ClPh	S	427.337	427
7	B		3,4-di-ClPh	S	465.306	465
8	B		3,4-di-ClPh	S	468.39	468
9	A+C		3,4-di-ClPh	S	399.283	399
10	A		3,4-di-ClPh	S	385.256	385
11	A		3,4-di-FPh	S	365.383	366
12	A		3,4-di-ClPh	S	398.292	398

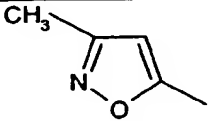
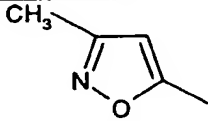
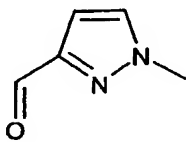
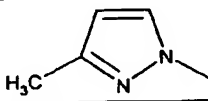
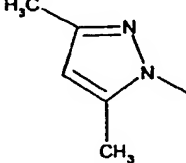
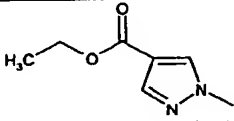
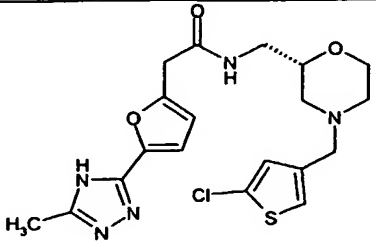
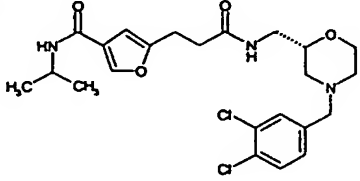
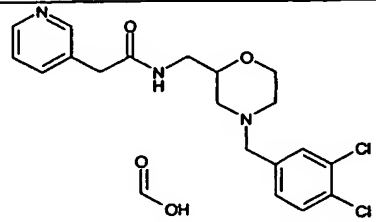
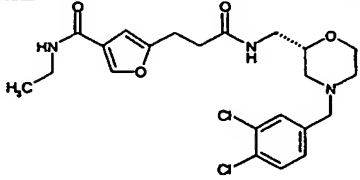
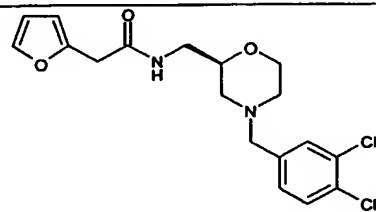
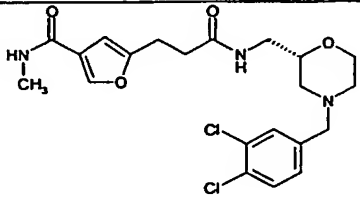
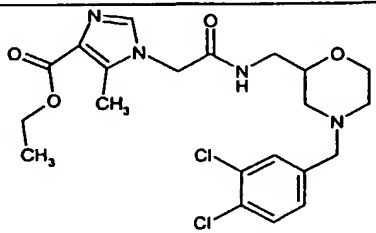
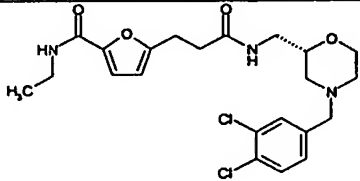
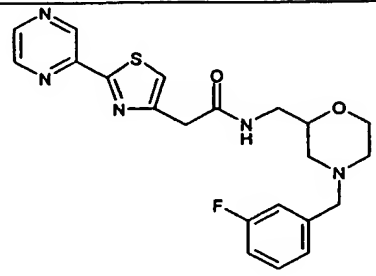
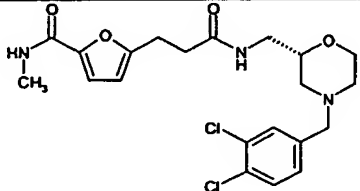
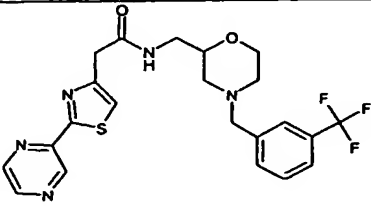
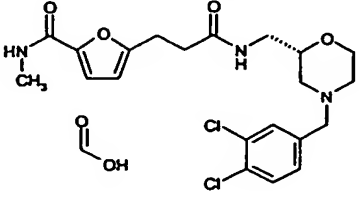
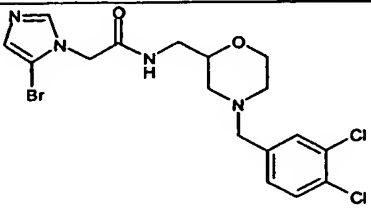
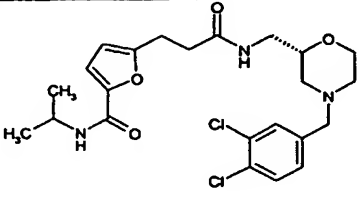
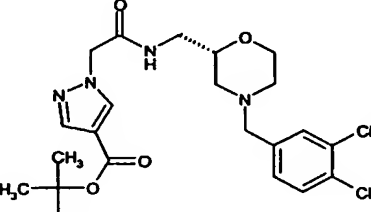
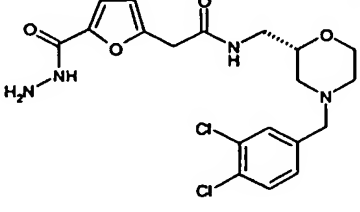
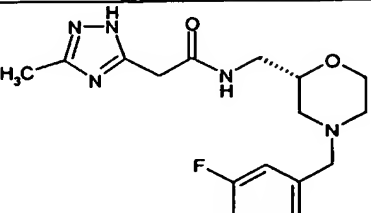
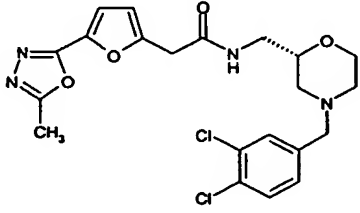
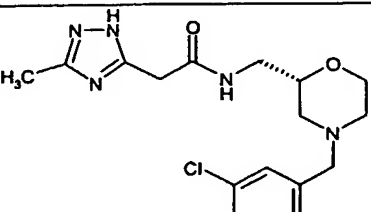
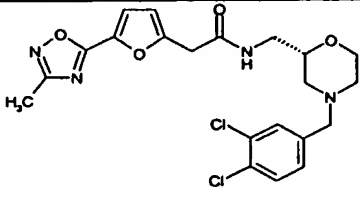
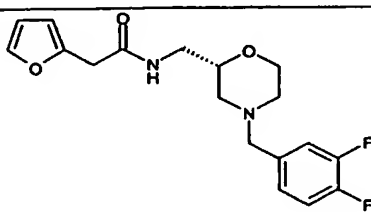
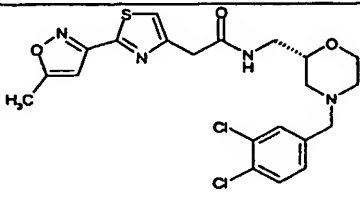
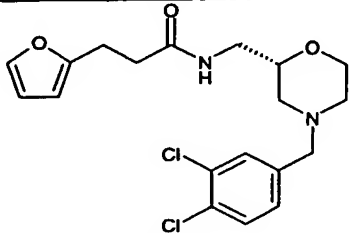
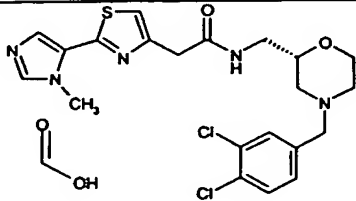
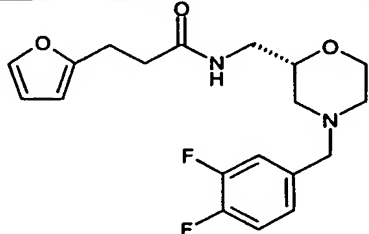
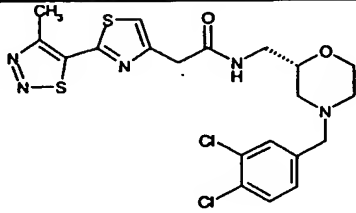
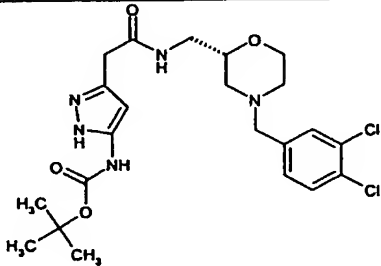
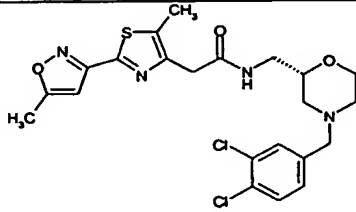
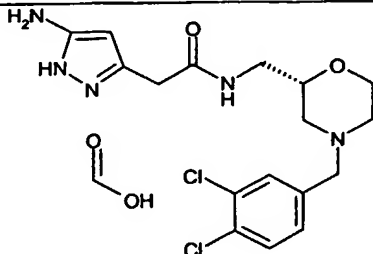
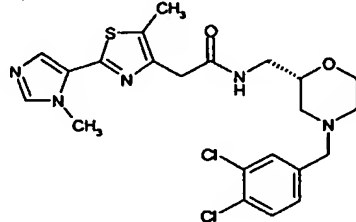
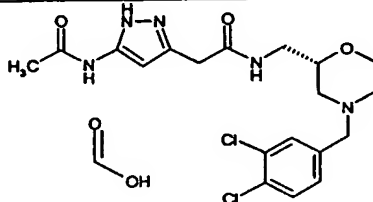
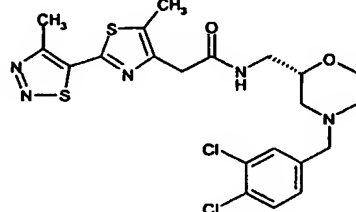
Ex. No.	Synthetic Method	R <sup>1</sup>	R <sup>2</sup>	Stereochem at position (*)	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) [M+H] <sup>+</sup> of lowest mass isomer unless otherwise indicated
13	A		3,4-di-FPh	S	365.383	366
14	A		3,4-di-ClPh	S	398.292	398
15	A		3,4-di-ClPh	S	411.291	411
16	A		3,4-di-ClPh	S	397.308	397
17	A		3,4-di-ClPh	S	411.335	411
18	A		3,4-di-ClPh	S	455.345	455

Table 2

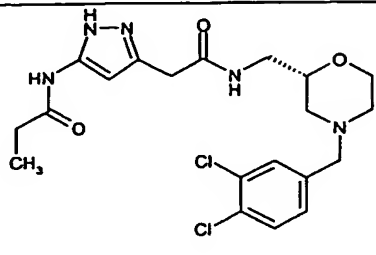
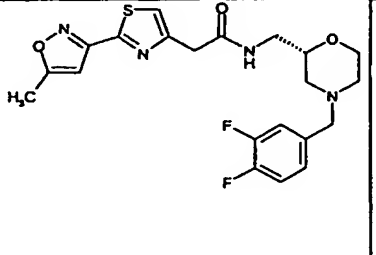
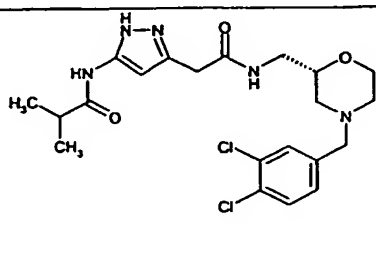
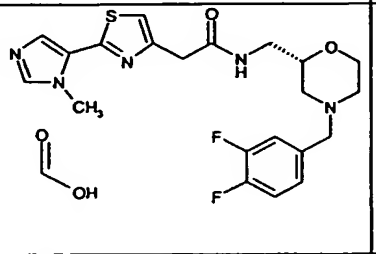
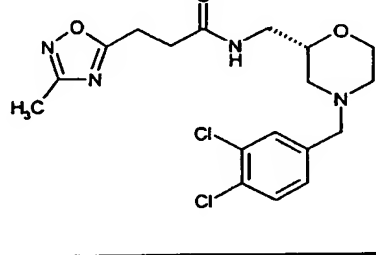
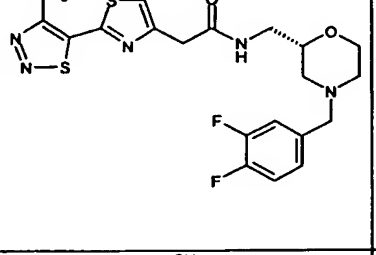
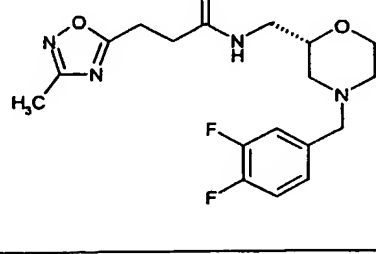
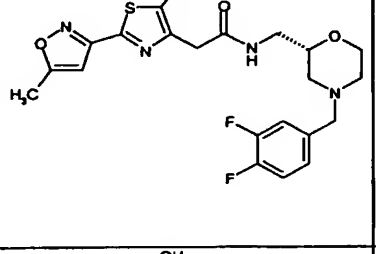
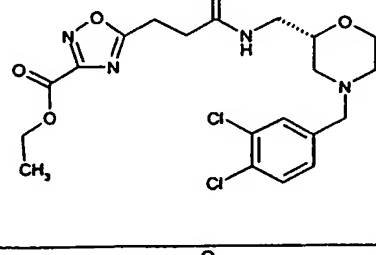
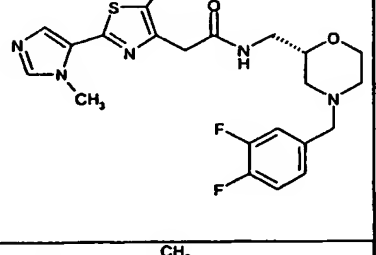
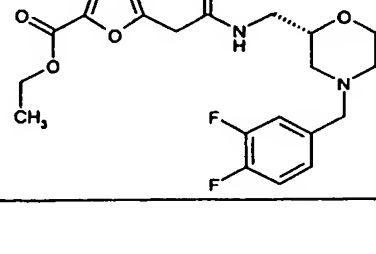
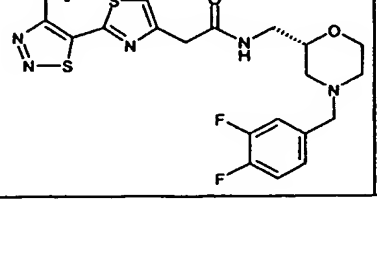
Ex.	Structure	Obs. [MH <sup>+</sup> ]	Ex.	Structure	Obs. [MH <sup>+</sup> ]
19		456	20		400
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23		484	24		414
25		424	26		469
27		438	28		455
29		452	30		541

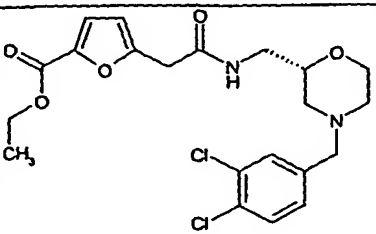
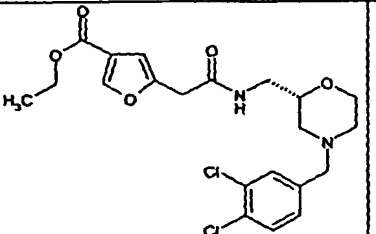
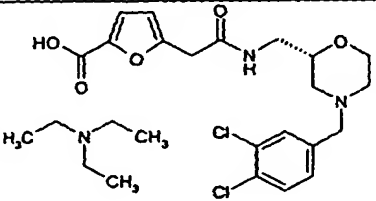
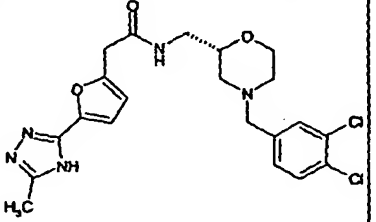
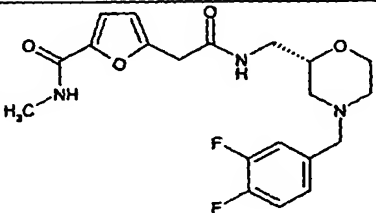
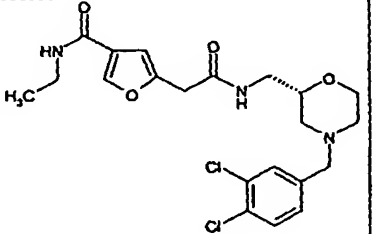
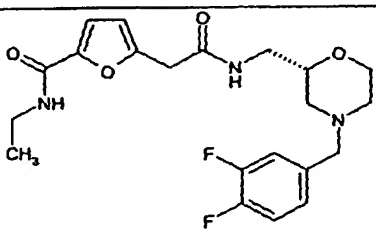
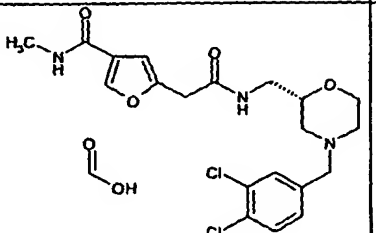
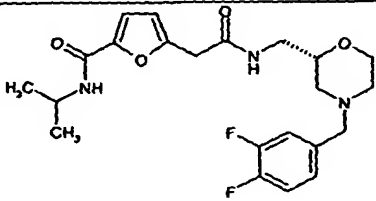
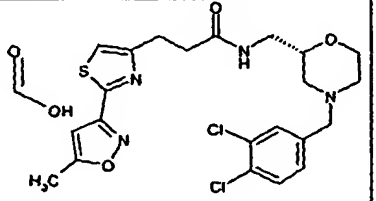
31		436	32		482
33		394	34		468
35		383	36		454
37		469	38		468
39		428	40		454

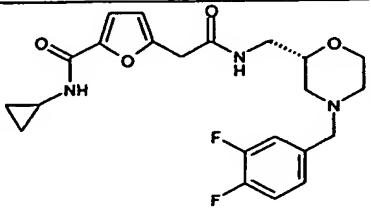
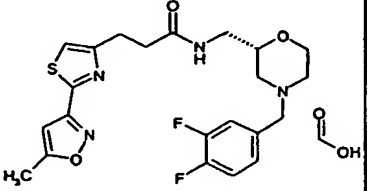
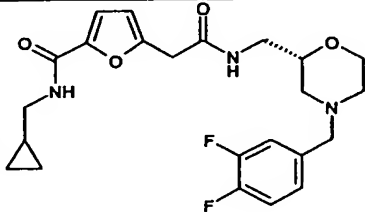
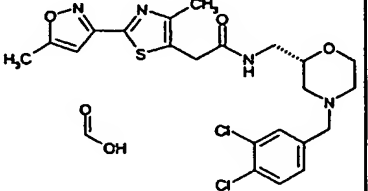
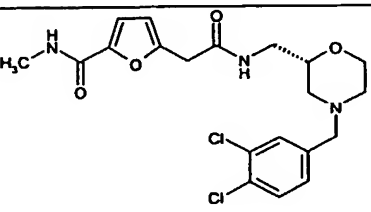
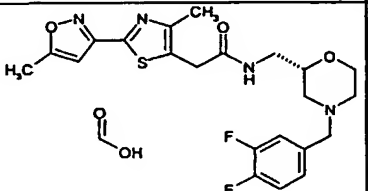
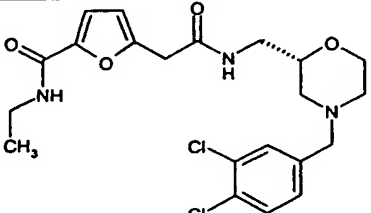
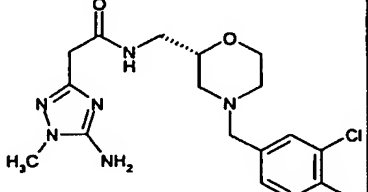
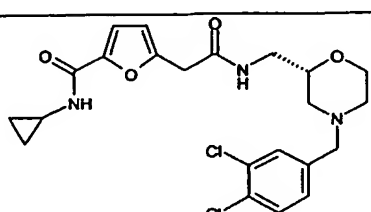
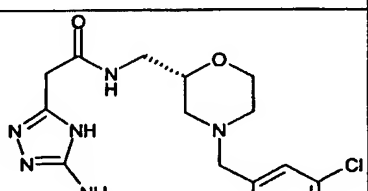
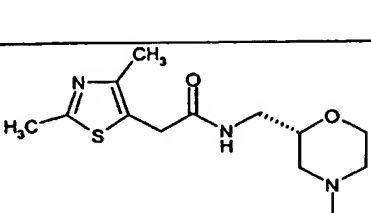
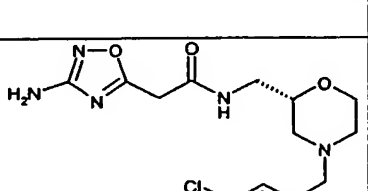
41		478	42		454
43		462	44		482
45		483	46		441
47		366	48		465
49		398	50		465
51		351	52		481

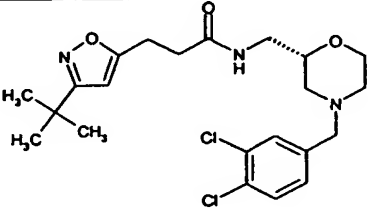
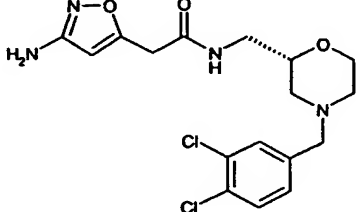
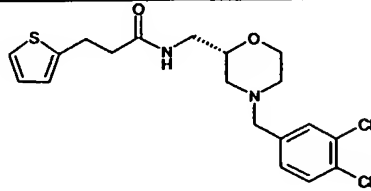
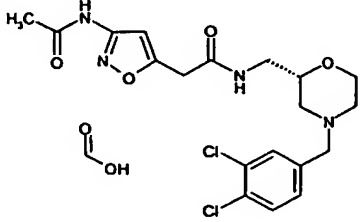
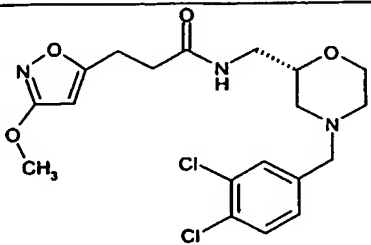
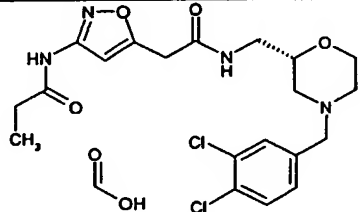
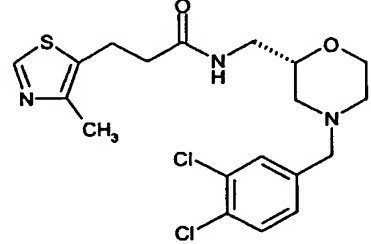
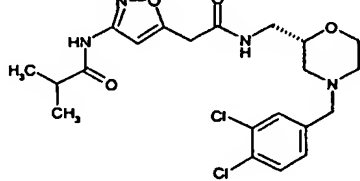
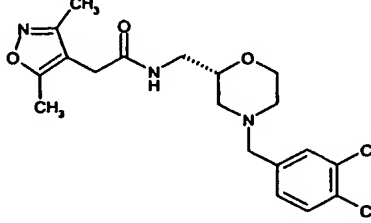
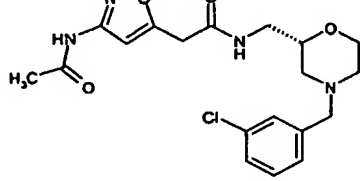
53		397	54		480
55		365	56		498
57		498	58		495
59		**	60		494
61		440	62		512

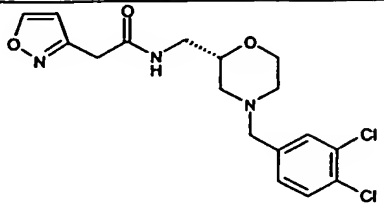
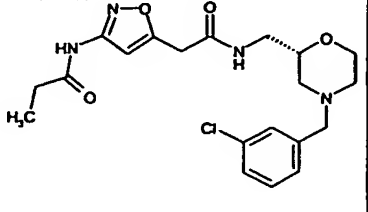
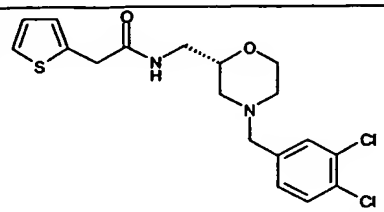
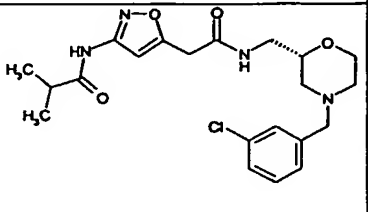
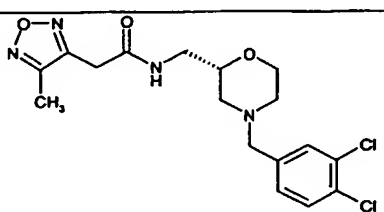


63		454	64		449
65		468	66		448
67		413	68		466
69		381	70		463
71		471	72		462
73		423	74		480

<b>75</b>		<b>455</b>	<b>76</b>		<b>455</b>
<b>77</b>		<b>427</b>	<b>78</b>		<b>464</b>
<b>79</b>		<b>408</b>	<b>80</b>		<b>454</b>
<b>81</b>		<b>422</b>	<b>82</b>		<b>440</b>
<b>83</b>		<b>436</b>	<b>84</b>		<b>495</b>

85		434	86		463
87		448	88		495
89		440	90		463
91		454	92		413
93		466	94		399
95		428	96		400

97		454	98		399
99		413	100		441
101		428	102		455
103		428	104		469
105		412	106		407

107		384	108		421
109		399	110		435
111		399			

Synthetic Method A was used for the preparation of Examples 19, 20, 21, 23, 24, 26, 28, 75, 76, 92, 94, 95, 97, 99, 101, 49, 52, 53, 54, 56, 57, 58, 60, 62, 29, 47, 51, 55, 64, 66, 68, 70, 72, 73, 74, 27, 96, 33, 35, 86, 90, 103, 105, 107, 109, 111, 41, 39, 25, 84, and 88.

Synthetic Method A+F+I+J+L was used for the preparation of Example 31.

Synthetic Method A+J was used for the preparation of Example 98.

Synthetic Method B (Alternative procedure 1) was used for the preparation of Examples 43 and 37.

10 Synthetic Method B (Alternative Procedure 2) was used for the preparation of Example 45.

Synthetic Method D was used for the preparation of Examples 61, 65, and 63.

Synthetic Method E was used for the preparation of Examples 102, 104, 106, 108, 110, and 100.

15 Synthetic Method F was used for the preparation of Examples 22 and 77.

Synthetic Method G was used for the preparation of Example 50.

Synthetic Method H was used for the preparation of Example 67, 71, and 69.

Synthetic Method I was used for the preparation of Examples 32, 34, 36, 38, 40, 42, 44, 79, 80, 81, 82, 83, 85, 87, 89, 91, 93, and 30.

20 Synthetic Method J was used for the preparation of Examples 59 and 46.

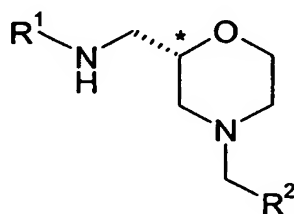
Synthetic Method K was used for the preparation of Example 48.

Synthetic Method L was used for the preparation of Example 78.

\*\* NMR data for Example 59

1H NMR (D<sub>4</sub>-MeOH 400MHz) 8.14 (1H,s) 7.53 (1H, s) 7.48 (1H,d) 7.27 (1H, d)  
5 3.86 (1H,m) 3.62 (2H,m) 3.53 (2H,s) 3.42 (2H,s) 3.24 (2H,m) 2.76 (1H,d) 2.68  
(1H,d) 2.23 (1H,m) 1.96 (1H,t)

Table 3

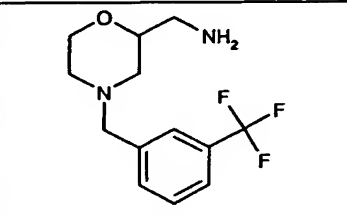
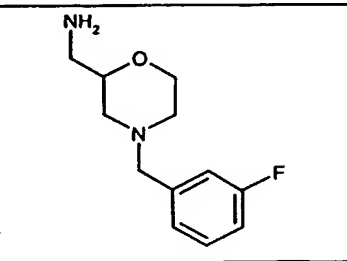
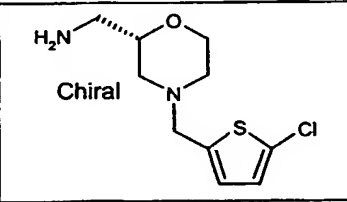
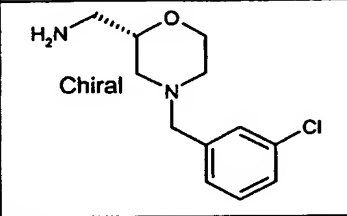
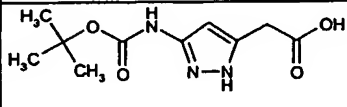
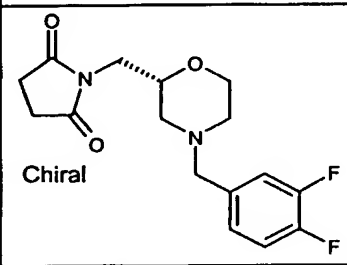
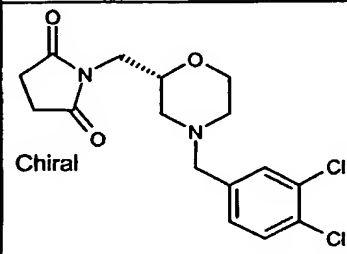


Description No.	R <sup>1</sup>	R <sup>2</sup>	Stereochem at position (*)
9	BrCH <sub>2</sub> CO-	3,4-di-ClPh	S

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Table 4

Description No.	Structure
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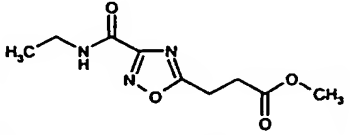
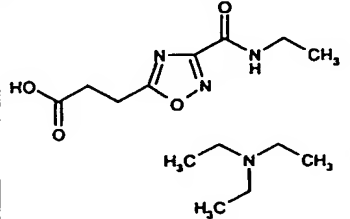
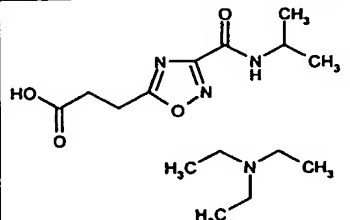
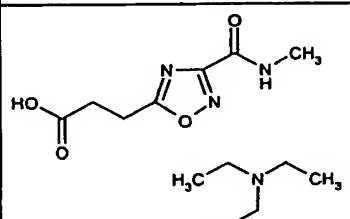
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45	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
46	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
47	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
48	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
49	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
50	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
51	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
52	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
53	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral
54	 <chem>CC(C)(CN(C)CC)CCNC(=O)CCc1cc(O)c(C(=O)O)oc1</chem> Chiral

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56	
57	
58	
59	